SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sotalol Hydrochloride 80mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80mg sotalol hydrochloride .

Excipient with known effect:

Each tablet contains 26.75mg 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 6.9mm–7.1mm and height of 2.8mm-3.2mm, 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 arrythmias:

- 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 hydrochloride 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 section 4.4).

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 β-adrenergic blocking properties, treatment with sotalol hydrochloride 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 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 to 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 - 640mg/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 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:

Creatinine clearance (ml/min)	**Adjusted doses**
>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 Cockroft 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 μmol/l, divide the value by 88.4 (1mg/dl = 88.4 μ mol/l).

Dosage in hepatically impaired patients
Since sotalol hydrochloride is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol hydrochloride. 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 hydrochloride tablets are contraindicated in the following:

- 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 myocardial infarction have been reported after abrupt discontinuation of therapy. Patients should be carefully monitored when discontinuing chronically administered sotalol hydrochloride, particularly those with ischaemic heart disease. If possible, the dosage should be gradually reduced over a period of one or two weeks. Because coronary artery disease is common and may be unrecognised in patients receiving sotalol hydrochloride, abrupt discontinuation in patients with arrhythmias may unmask latent coronary insufficiency. In addition, hypertension may develop.

Proarrhythmia
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 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 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 320mg. The incidence more than doubled at higher doses.

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

Electrolyte disturbances
Sotalol hydrochloride 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 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. The adverse results of clinical trials involving antiarrhythmic drugs (i.e. apparent increase in mortality) suggest that 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 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 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
Sotalol hydrochloride 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 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 section 4.2).

Psoriasis

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

Lactose
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 antiarrhythmics such as amiodarone and bepridil are not recommended as concomitant therapy with sotalol hydrochloride, because of their potential to prolong refractoriness (see section 4.4). The concomitant use of other beta-blocking agents with sotalol hydrochloride may result in additive Class II defects.

Other drugs prolonging the QT-interval
Use with great caution with drugs that prolong QT-interval e.g. phenothiazines, tricyclic antidepressants, terfenadine, astemizole or fluoroquinalones. Drugs that have been associated with an increased risk of ventricular arrhythmias, particularly torsades de pointes include erythromycin IV, halofantrine, pentamidine and fluoroquinolones.

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

Calcium channel blockers
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 section 4.4).

Other Potassium-depleting diuretics
Amphotericin B (IV), corticosteroids (systemic administration) and some laxatives may be associated with hypokalaemia. Potassium levels should be monitored and corrected appropriately during concomitant administration with sotalol hydrochloride.

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-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 tubocurarine
The 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 when measured by photometric methods. Patients suspected of having phaeochromocytoma and who are being treated with sotalol should have their urine screened utilizing the HPLC assay with solid phase extraction.

4.6 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. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. 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.

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).

4.8 Undesirable effects

Sotalol hydrochloride 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.

The following are adverse events considered related to therapy with sotalol hydrochloride:

Cardiac disorders:
Common: Bradycardia, dyspnoea, chest pain, palpitations, oedema, Electrocardiogram (ECG) abnormal, hypotension, arrhythmia, syncope, presyncope, cardiac failure

Skin and subcutaneous tissue disorders:
Common: Rash
Frequency unknown: Alopecia, hyperhidrosis

Gastrointestinal disorders:
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence

Musculoskeletal, connective tissue and bone disorders:
Common: Muscle spasms

Nervous system disorders:
Common: Headache, dizziness, fatigue, asthenia, lightheadedness, 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

Blood and lymphatic system disorders:
Frequency unknown: Thrombocytopenia

In clinical trials, 3256 patients with cardiac arrhythmias (1363 with sustained ventricular tachycardia) received oral sotalol hydrochloride, 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:

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 = 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 hydrochloride are listed 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 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. 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 (2-16g) of sotalol hydrochloride, the following clinical findings were seen: hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia and torsades de pointes.

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

Heart block of second or 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 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 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 QT_C (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 25mg, Class III effects are usually seen at daily doses of greater than 160mg.

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 renin-suppressive effect of sotalol is significant both at rest and during exercise. Like other beta-adrenergic blocking agents, sotalol hydrochloride produces a gradual but significant reduction in both systolic and diastolic blood pressures in hypertensive patients. 24-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 40-640mg/day sotalol hydrochloride 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 section 4.2). 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 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

Tillomed Laboratories Ltd

220 Butterfield,

Great Marlings,

Luton,
LU2 8DL,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0071

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/03/1998 / 27/03/2009

10 DATE OF REVISION OF THE TEXT

25/08/2020