SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sotalol 80 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg Sotalol hydrochloride.

Excipient(s) with known effect
For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Round, white to off-white, flat, bevelled tablets with the Chatfield logo on one side and a breakline and SOT80 imprinted on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sotalol 80 mg 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

Adults
The recommended initial dose is 40 mg either as a single dose or in two divided doses taken at 12 hour intervals. The dosage of Sotalol 40 mg Tablets should be gradually increased according to the patient's response. Adjustments to dosage should be made after steady-state has been attained, usually after 2-3 days, and to allow monitoring of QT intervals. Proarrhythmias can occur at initiation and at each upward adjustment of dosage.

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 to 640 mg a day but these doses should only be used under specialist supervision and should only be prescribed when the potential benefit outweighs the increased risk of adverse reactions, particularly proarrhythmias, (see section 4.4).

Paediatric population
Sotalol is not intended for administration to children.

Dosage in Renally Impaired Patients:
Because Sotalol is excreted mainly in urine, patients with a creatinine clearance of less than 60 ml/min should be prescribed with a reduced dose according to the following:

Creatinine clearance: >60 ml/min: Recommended dose.

Creatinine clearance: 30-60 ml/min: Half recommended dose.

Creatinine clearance: 10-30 ml/min: Quarter recommended dose.

Creatinine clearance: <10 ml/min: Not recommended.

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: as above x 0.85

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

Dosage in Hepatically Impaired Patients:
No dosage adjustment is necessary in patients with impaired hepatic function.

Method of administration

Sotalol 80 mg Tablets are for oral administration in adults.

The start of treatment and adjustment of the dose should only follow an appropriate medical evaluation including ECG control with the measurement of the corrected QT interval and assessment of renal function, electrolyte balance and concomitant medication, (see section 4.4).

As with other antiarrhythmic agents, it is recommended that Sotalol 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 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).

4.3 Contraindications

Cardiovascular

Sotalol is contra-indicated in patients with the following conditions. Sick sinus syndrome, second or third degree AV heart block unless fitted with a functional pacemaker, congenital or acquired long QT syndromes, torsades de pointes, symptomatic sinus bradycardia, uncontrolled congestive heart failure, cardiogenic shock, anaesthesia that produces myocardial depression, hypotension (except due to arrhythmia), severe peripheral circulatory disturbances including those associated with Raynaud's phenomenon.

Respiratory

History of chronic obstructive airway disease, bronchial asthma or bronchospasm

Hypersensitivity

Hypersensitivity to any of the ingredients of the tablet

Untreated phaeochromocytoma, metabolic acidosis, renal failure (creatinine clearance < 10 ml/min)

4.4 Special warnings and precautions for use

Abrupt Withdrawal

Patients should be carefully monitored when discontinuing chronic Sotalol administration, particularly those with ischaemic heart disease. Dosage should be gradually reduced over a period of 1 to 2 weeks and 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.

Pro-arrhythmias

Sotalol may aggravate pre-existing arrhythmias or provoke new arrhythmias. Sotalol should be used with caution in patients with Raynauld's phenomenon. Drugs that prolong the QT interval may cause torsades de pointes, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. The risk of torsades de pointes is associated with prolongation of the QT interval, reduction of heart rate, reduction in serum potassium and magnesium, high plasma Sotalol concentrations and concomitant use of Sotalol with other medicines associated with this condition, (see section 4.5). Females may be at increased risk of developing torsades de pointes.

The incidence of torsades de pointes is dose dependent and usually occurs within 7 days of initiation of treatment or after increasing 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.

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.

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. Caution is advised if the QT_c exceeds 500 msec whilst on therapy. When the QT_c-interval exceeds 550 msec dosage should be reduced or therapy with Sotalol discontinued. 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 should not be used in patients with hypokalaemia or hypomagnesaemia prior to correction of the imbalance as this can exaggerate the degree of QT prolongation, and increase the potential for torsades de pointes. Special care should be given to electrolyte and acid-base balance in patients with severe or persistent diarrhoea and in patients receiving concomitant drugs that are likely to reduce serum potassium and/or magnesium levels.

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 at all stages of therapy. Sotalol should not be used 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. 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 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 when administering Sotalol tablets to patients with diabetes (especially labile diabetes) or a history of spontaneous hypoglycaemia as beta-blockade may mask some important signs of acute hypoglycaemia such as tachycardia.

Thyrotoxicosis
Beta-blockade may mask certain clinical symptoms of hyperthyroidism, (e.g. tachycardia). Sotalol should not be withdrawn abruptly from patients suspected of developing thyrotoxicosis, as this may exacerbate the 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.

4.5 Interaction with other medicinal products and other forms of interaction

Clonidine
Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, in combined therapy with clonidine, Sotalol should be withdrawn several days before slowly withdrawing clonidine.

Antiarrhythmics
Class 1 antiarrhythmic agents such as disopyramide, procainamide, amiodarone, bepridil or quinidine are not recommended as concomitant therapy with Sotalol, because of their potential to prolong refractoriness (see section 4.4). The concomitant use of other betablocking agents with Sotalol may result in additive Class II effects.

Other drugs that prolong the QT-interval
Sotalol should be used with great caution in conjunction with other drugs that also prolong QT-interval such as phenothiazines, tricyclic antidepressants, terfenadine, astemizole. Other drugs that have been associated with an increased risk for torsades de pointes include halofantrine, pentamidine, quinolone antibiotics and erythromycin IV.

Calcium-channel blocking drugs
Concomitant use of beta-blocking agents with calcium-channel blockers has resulted in hypotension, bradycardia, conduction defects, and cardiac failure. Severe hypotension and heart failure is a risk with nifedipine and possibly other dihydropyridines.

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. Asystole, severe hypotension, and heart failure have also occurred with verapamil.

Cardiac glycosides
Single and multiple doses of Sotalol do not significantly affect serum digoxin levels. Proarrhythmic events such as AV block and bradycardia are more common in patients also receiving cardiac 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 betablockers may increase auriculo-ventricular conduction time.

Antimalarials
There is an increased risk of bradycardia with mefloquine.

Catecholamine-depleting agents

Concomitant use of catecholamine-depleting drugs, such as reserpine, guanethidine or alpha methyldopa, with a betablocker may produce an excessive reduction of resting sympathetic nervous tone. Patients require close monitoring for evidence of hypotension and/or marked bradycardia, which may produce syncope.

Potassium depleting drugs
Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsade de pointes (see section 4.4).
Other potassium-depleting drugs
Concomitant use with diuretics, laxatives, corticosteroids (systemic administration), and Amphotericin B (IV route), may also be associated with hypokalaemia; potassium levels should be monitored and corrected appropriately during concomitant administration with Sotalol.

Beta-agonists
Beta-agonists should not be administered with Sotalol but if concomitant therapy is necessary the dosage of the beta-agonist may need to be increased.

Neuromuscular-blocking agents
Neuromuscular blockade of tubocurarine is prolonged by beta-blocking agents.

Insulin and oral hypoglycaemics
The dosage of antidiabetic drugs may require adjustment if hypoglycaemia occurs. The symptoms of hypoglycaemia (e.g. tachycardia) may be masked by beta-blocking agents.

Sympathomimetics
Severe hypertension with adrenaline and noradrenaline and possibly with dobutamine

Laboratory tests
Laboratory assays for urinary metanephrine should be performed by HPLC as photometric measurements may be high when Sotalol is present. Patients suspected of having phaeochromocytoma and who are treated with Sotalol should have their urine screened utilizing the HPLC assay with solid phase extraction.
Anxiolytics and hypnotics
Enhanced hypotensive effects have been observed with concomitant use of anxiolytics and hypnotics.

NSAIDs
The risk of ventricular arrhythmias is increased with concomitant use of Sotalol and NSAIDs.

Phenothiazines
Concomitant use of Sotalol with phenothiazines and pimozide increases the risk of ventricular arrhythmias.

Peripheral and cerebral vasodilators
Peripheral vasoconstriction is increased with ergotamine. Possible severe postural hypotension with moxisylyte

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

Others
The hypotensive effect of Sotalol is antagonised by corticosteroids, carbenoxolone, oestrogens and combined oral contraceptives. The risk of ventricular arrhythmias is

increased with concomitant use of Sotalol and terfenadine, mizolastine, possibly pilocarpine and tropisetron. Enhanced hypotensive effects have been observed with concomitant use of aldesleukin and alprostadil.

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 has been shown to cross the placenta and is found in amniotic fluid. Evidence of foetal damage has been demonstrated and is a finding, which occurs with drugs with class III anti-arrhythmic activity. These may induce hypoxia related abnormalities and damage to the foetus, which may occur during or after the first trimester of pregnancy. Beta-blockers reduce placental perfusion, which may result in intra-uterine 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.

Its use in pregnancy should be avoided unless the potential benefits outweigh the possible risk to the foetus. Monitoring of the baby for 48-72 hours is recommended 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 treatment with Sotalol.

4.7 Effects on ability to drive and use machines

If affected by dizziness or fatigue the patient should be advised against driving or operating machinery.

4.8 Undesirable effects

The most common adverse effects are due to the beta-blockade properties of Sotalol. These effects do not usually necessitate interruption or withdrawal of treatment and normally disappear when dosage is reduced.

Serious adverse effects are due to pro-arrhythmia, including torsades de pointes, (see section 4.4).

Patients with a history of anaphylactic reactions may be more prone to severe adverse reactions.

The following are adverse events considered related to therapy, occurring in 1% or more of patients treated with Sotalol.

Side-effects include:

Blood and the lymphatic system disorders
Purpura, thrombocytopenia

Psychiatric disorders
Sleep disturbances, depression, mood changes, anxiety, psychoses

Nervous system disorders
Dizziness, light-headedness, headache, paraesthesia, taste abnormalities

Eye disorders
Visual disturbances

Ear and labyrinth disorders
Hearing disturbances, vertigo

Cardiac disorders
Bradycardia, palpitations, ECG abnormalities, proarrhythmia- including torsades de pointes, heart failure

Vascular disorders
Hypotension, syncope, presyncope

Respiratory, thoracic and mediastinal disorders
Dyspnoea

Sotalol should be used with caution in patients with a history of wheezing or asthma, as there is a risk of bronchospasm with beta-blockade

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

Skin and subcutaneous tissue disorders
Rash, exacerbation of the symptoms of psoriasis vulgaris, alopecia

Musculoskeletal, connective tissue and bone disorders
Muscle cramp

Reproductive system and breast disorders
Sexual dysfunction

General disorders and administration site conditions
Chest pain, oedema, fatigue, asthenia, fever

In trials of patients with cardiac arrhythmia, the most common adverse events leading to discontinuation of Sotalol were fatigue 4%, bradycardia (<50 bpm) 3%, dyspnoae 3%, proarrhythmia 2%, asthenia 2%, and 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.

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
The most common symptoms of overdose are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycaemia. Prolonged QT interval, premature ventricular complexes, A-V block, ventricular tachycardia and torsades de pointes are also seen after intentional overdosage (2-16 g).

Management
If overdosage occurs, therapy with Sotalol should be discontinued and the patient observed closely. In addition, if required, appropriate therapeutic measures administered.

- *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: C07A A07

Mechanism of action
D, l-sotalol is a non-selective, hydrophilic beta-adrenergic blocking agent, devoid of intrinsic sympathomimetic activity and membrane-stabilizing properties.

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 duration of the myocardial action potential and the QT interval by delaying the repolarisation phase. It has no effect on the depolarisation phase.

Pharmacodynamic effects
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 1-isomer is responsible for virtually all of the beta-blocking activity.

Clinical efficacy and safety
Significant beta-blockade may occur at oral daily doses as low as 25 mg but class III effects are usually seen at daily doses greater than 160 mg.

The beta-adrenergic blocking activity of Sotalol causes a reduction in heart rate (negative chronotropic effect) and a limited reduction in the force of contraction

which both reduce cardiac work. Like other beta-blockers, Sotalol inhibits rennin release. The renin-suppressive effect of Sotalol is significant both at rest and during exercise. 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

Absorption
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
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.

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

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Maize starch
Povidone K30
Sodium starch glycollate, Type A
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

PVC / PVDC / aluminium blister pack containing 14, 15, 28, 30, 50, 60, 84, 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Chelonia Healthcare Limited

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3rd Floor, 1060 Nicosia

Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0151

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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