Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sotoger 80mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sotalol hydrochloride 80 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets
White flat bevel-edged tablet with “SL” breakline “80” on one side and blank on the reverse, approximately 7mm in diameter. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sotalol is indicated in adults 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

The initiation of treatment or changes in dosage with Sotoger 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 Sotoger 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 Sotoger 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).

The following dosing schedule can be recommended:

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

Oral dosage of Sotoger 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; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, particularly proarrhythmias (see section 4.4).

Renal impairment
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 Sotoger Dose
30 – 60	½ recommended Sotoger Dose
10 – 30	¼ recommended Sotoger Dose
< 10	Avoid

Due to a high risk of proarrhythmias in patients with creatinine clearance less than 30 ml/min, care should be taken with sotalol administration in these patients.

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: $$\text{idem} \times 0.85$$

When serum creatinine is given in micromol/l, divide the value by 88.4

(1 mg/dl =88.4 micromol/l).

Hepatic impairment

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.

Paediatric population

The safety and effectiveness of Sotoger in children under 18 has not been established. There is no relevant use of sotalol in the paediatric population.

Method of administration

For oral administration only.

4.3 Contraindications

Sotoger should not be used where there is any evidence of:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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
- bradycardia < 50 bpm
- untreated phaeochromocytoma
- hypotension (except due to arrhythmia)
- Raynaud's phenomenon and severe peripheral circulatory disturbances
- history of chronic obstructive airway disease or bronchial asthma
- metabolic acidosis
- renal failure (creatinine clearance < 10 ml/min)
- The intravenous administration of verapamil or diltiazem calcium antagonists or other antiarrhythmic agents (such as disopyramide) is contraindicated in patients treated with sotalol hydrochloride (except in the case of intensive care medicine).

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 III antiarrhythmic drugs 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, (e.g. as a consequence of diuretic use), high plasma sotalol concentrations (e.g. as a consequence of overdosage or renal insufficiency), and with the concomitant use of sotalol and other medications such as antidepressants and Class I antiarrhythmics which have been associated with torsades de pointes (see section 4.5). Females may be at increased risk of developing torsades de pointes.

ECG monitoring immediately prior to or following the episodes usually reveals a significantly prolonged QT interval and a significantly prolonged QTc interval. In clinical trials sotalol generally has not been initiated to patients whose pretreatment QTc interval exceeded 450 msec. Sotalol should be titrated very cautiously in patients with prolonged QT intervals.

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 terminates spontaneously in the majority of patients. Although most episodes of torsades de pointes are self-limited or associated with symptoms (e.g. syncope), and they can progress to ventricular fibrillation.

Clinical studies for arrhythmia: During clinical trials, 4.3% of 3257 patients with arrhythmias experienced a new or worsened ventricular arrhythmia, including sustained ventricular tachycardia (approximately 1%) and torsade de pointes (2.4%). In addition, in approximately 1% of patients, deaths were considered possibly drug-related. In patients with other, less serious, ventricular arrhythmias and supraventricular arrhythmias, the incidence of torsade de pointes was 1% and 1.4%, respectively.

Serious proarrhythmias including torsade de pointes were dose related as indicated below:

Percent Incidence of Serious Proarrhythmias * by Dose For Patients With Sustained VT/VF		
Daily Dose (mg)	**Incidence of Serious Proarrhythmias***	**Patients (n)**
1-80	0	(0/72)
81-160	0.5%	(4/838)
161-320	1.8%	(17/960)
321-480	4.5%	(21/471)
481-640	4.6%	(15/327)
>640	6.8%	(7/103)

*Torsade de pointes or new sustained VT/VF

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 QTC 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; events tend to occur within 7 days of initiating therapy or with an increase in dose. Initiating therapy at 80 mg with gradual upward dose titration thereafter reduces the risk of proarrhythmia. In patients already receiving sotalol it should be used with caution if the QTC is greater than 500 msec 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: Sotoger 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. Patients with a history of severe hypersensitivity reactions and patients who are currently undergoing desensitization therapy are at higher risk of developing excessive anaphylactic reactions. Sotalol hydrochloride should therefore only be administered to such patients if absolutely indicated. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

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

Sotalol can be administered with caution to patients with obstructive respiratory disorders provided that adequate supervision is maintained. If increased airways resistance develops consideration must be given to discontinuation of the beta-blocker, depending on the degree of airways resistance and the benefit derived from beta-blockade.

Diabetes Mellitus: Sotoger 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.

Hepatic Impairment*:* Since sotalol is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol.

Renal Impairment: Sotalol is mainly eliminated via the kidneys through glomerular filtration and to a small degree by tubular secretion. There is a direct relationship between renal function, as measured by serum creatinine or creatinine clearance, and the elimination half-life of sotalol and its urinary excretion. The dose should be adjusted in patients with renal impairment (see section 4.2).

Pheochromocytoma: Sotalol hydrochloride should not be administered to patients with pheochromocytoma unless they are concomitantly receiving alpha-blocker therapy.

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

Antiarrhythmics: Class Ia antiarrhythmic drugs, such as disopyramide, quinidine, procainamide and flecainide and other Class III antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with Sotoger, because of their potential to prolong refractoriness (see section 4.4). The concomitant use of other beta-blocking agents with Sotoger may result in additive Class II effects (reduction in blood pressure and heart rate).

Other drugs prolonging the QT-interval: Sotoger should be given with extreme caution in conjunction with other drugs known to prolong the QT-interval such as phenothiazines, tricyclic or tetracyclic antidepressants (imipramine, maprotiline), antihistamine (terfenadine and astemizole). Other drugs that have been associated with an increased risk for torsades de pointes include macrolide antibiotics, halofantrine, haloperidol, pentamidine, and quinolone antibiotics.

Patients may experience an excessive drop in blood pressure with concomitant use of sotalol hydrochloride and tricyclic antidepressants, barbiturates, phenothiazines, opioids, antihypertensives, diuretics or vasodilators.

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 torsades de pointes (see section 4.4).

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 Sotoger.

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 (such as salbutamol, terbutaline and isoprenaline) 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 utilizing 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, Sotoger should be used in pregnancy only if the potential benefits outweigh the possible risk to the foetus. Sotalol should be discontinued 48 – 72 hours before calculated delivery. If this is not possible the neonate should be kept under surveillance for 48 – 72 hours post- partum for signs and symptoms of beta-blockage (e.g. heart and lung complications).

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. If sotalol hydrochloride treatment is taken during lactation, babies must be monitored for signs of beta blockade.

Fertility
There is no clinical data on fertility from the use of this medicine. Data on fertility in animals are not available.

4.7 Effects on ability to drive and use machines

There is 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 is well tolerated in the majority with the most frequent adverse effects arising from 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) not known (cannot be estimated from the available data).

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

Blood and lymphatic system disorders
Not known: thrombocytopenia

Psychiatric disorders
Common: depression, confusion, sleep disorder, mood altered, anxiety
Not known: hallucinations, abnormal dreams

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

Eye disorders

Common: Visual disturbances
Not known: Blurred vision, conjunctivitis, keratoconjunctivitis, reduced lacrimation (particularly in wearers of contact lenses)

Ear and labyrinth disorders
Common: hearing disturbances

Cardiac disorders
Common: Bradycardia, dyspnoea, chest pain, palpitations, oedema, ECG abnormalities, Torsade de pointes, QT interval prolongation, AV conduction disorder, ventricular tachycardia, exacerbation in angina pectoris, arrhythmia, syncope, cardiac failure, presyncope
Not known: Cardiac arrest

Vascular disorders
Common: hypotension, exacerbation of peripheral occlusive disease, cold limbs

Gastrointestinal disorders
Common: Nausea/vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence
Not known: dry mouth

Skin and subcutaneous tissue disorders
Common: Rash, skin reactions
Not known: drugs with beta-blocking activity may trigger psoriasis, exacerbate this condition or give rise to psoriatic exanthema, alopecia,hyperhidrosis.

Musculoskeletal and connective tissue disorders
Common: Muscle spasms

Reproductive system and breast disorders
Common: Sexual dysfunction, impotence

General disorders and administration site conditions
Common: Pyrexia, fatigue, asthenia

Metabolism and nutrition disorders
Not known: Increase in total cholesterol and triglyceride levels, reduction in HDL cholesterol, hypoglycemia.

In clinical trials, 3257 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:

Patient Populations (n = 3,257)*			
	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%

* One patient had sinus tachycardia
VT = ventricular tachycardia; VF = ventricular fibrillation; NSVT = nonsustained 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie.

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.

Sotoger have 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, Sotoger produce 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 Sotoger 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.

Biotransformation and 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.

Patients with renal impairment
Lower doses are necessary in conditions of renal impairment (see section 4.2).

Older people
Age does not significantly alter the pharmacokinetics, although impaired renal function in older people can decrease the excretion rate, resulting in increased drug accumulation.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate Anhydrous
Maize Starch
Povidone K30
Sodium Starch Glycolate (Type A)
Talc
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Securitainer or HPDE Bottle: 5 years
Blister: 4 years

6.4 Special precautions for storage

Polypropylene Containers or HPDE Bottle
Keep the container tightly closed in order to protect from light.

Blister Packs
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Securitainer: (Polypropylene container with a polyethylene push-on, tamper evident closure and a low-density polyethylene Jayfilla)

Registered pack sizes: 20, 28, 30, 40, 50, 60, 100 & 300

Or
HDPE Bottle: (Opaque High-Density Polyethylene (HDPE) bottle with a plastic screw cap with aluminium liner)

Registered pack size: 100

Blister Packs: Opaque PVC bonded to aluminium foil by heat seal lacquer.

Registered pack sizes: 20, 28, 30, 40, 50, 60, 90, 100 & 300

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
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8 MARKETING AUTHORISATION NUMBER

PA23266/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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