

NEW ZEALAND DATA SHEET

SOTALOL



1. Product Name

SOTALOL, 80 mg and 160 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 80 mg or 160 mg of sotalol hydrochloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

The 80 mg tablet is round, white, flat bevel edged, 7 mm in diameter, debossed SL/80 on one side and plain on the other.

The 160 mg tablet is round, white, flat bevel edged, 9.5 mm in diameter, debossed SL/160 on one side and 'α' on the other.

4. Clinical Particulars

4.1 *Therapeutic indications*

Sotalol hydrochloride is indicated for use in the prevention and treatment of supraventricular and ventricular arrhythmias.

4.2 *Dose and method of administration*

Dose

Sotalol hydrochloride is administered orally for the prevention and treatment of arrhythmias.

As with other antiarrhythmic agents, sotalol hydrochloride should be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm. The dosage must be individualised for each patient on the basis of therapeutic response and tolerance. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dosage adjustment.

Oral dosage of sotalol hydrochloride should be adjusted gradually allowing two to three days between dosing increments in order to attain steady-state and to allow monitoring of QT intervals. Graded dose adjustment will help prevent the use of doses which are higher than necessary to control the arrhythmia. The recommended initial oral dosing schedule is 160 mg daily, given in two divided doses at approximately 12-hour intervals. This dose may be increased, if necessary, after appropriate evaluation to 240 or 320 mg/day. In most patients, a therapeutic response is obtained at a total daily dose of 160-320 mg/day, given in 2 divided doses. 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.

Because of the long elimination half-life of sotalol hydrochloride, dosing on more than a twice daily regimen is not usually necessary.

Special populations

Renal impairment

As sotalol is primarily excreted by the kidneys, a dosage adjustment should be made.

Method of administration

Sotalol hydrochloride should be taken preferably 1-2 hours before meals.

4.3 Contraindications

- History of bronchospasm (e.g. bronchial asthma) or chronic obstructive airway disease.
- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm.
- Right ventricular failure secondary to pulmonary hypertension.
- Significant right ventricular hypertrophy.
- Sinus bradycardia (less than 45-50 beats/minute).
- Second and third degree AV block or sick sinus syndrome unless a functioning pacemaker is present.
- Shock (including cardiogenic and hypovolaemic shock).
- Uncontrolled congestive heart failure.
- Severe renal impairment (CrCl <10 mL/min).
- Congenital or acquired long QT syndromes.
- Hypersensitivity to sotalol hydrochloride or to any of the excipients listed in section 6.1.
- Anaesthesia that produces myocardial depression.

4.4 Special warnings and precautions for use

No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with supraventricular or asymptomatic ventricular arrhythmias. Since most antiarrhythmic drugs have the potential to cause proarrhythmias or increase the incidence of sudden death, physicians should carefully consider the risks and benefits of antiarrhythmic therapy in these patients.

Proarrhythmia

Post-marketing experience

The most dangerous adverse effect of antiarrhythmic drugs is the aggravation of pre-existing arrhythmias or the provocation of new arrhythmias. The 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 in heart rate, reduction in serum potassium and magnesium (e.g. as a consequence of diuretic use), high plasma drug concentration (eg. 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. Females appear to 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 hydrochloride generally has not been initiated to patients whose pretreatment QTc interval exceeded 450 msec. Sotalol hydrochloride should be titrated very cautiously in patients with prolonged QT intervals.

Torsades de pointes is dose-dependent, usually occurs early after 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 (eg. syncope), 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 torsades 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 torsades de pointes was 1% and 1.4% respectively.

Serious proarrhythmias including torsades 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)

* Torsades de Pointes or New Sustained VT/VF.

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 ($\approx 7\%$).

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 twice daily with gradual upward dose titration thereafter reduces the risk of proarrhythmia (see section 4.2). Sotalol hydrochloride should be used with caution if the QTc is greater than 500 msec on-therapy, and serious consideration should be given to reducing the dose or discontinuing therapy when the QT 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.

Cardiac failure

Beta-blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency, or unsuspected cardiomyopathy. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If cardiac failure persists, sotalol hydrochloride should be discontinued (see section 4.4).

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.

(NOTE: Although congestive heart failure has been considered to be a contraindication to the use of beta-blockers, there is growing literature on the experimental use of beta-adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs, beta-blockers should not normally be prescribed for heart failure outside specialist centres).

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 hydrochloride should be avoided in patients with left ventricular ejection fractions $\leq 40\%$ without serious ventricular arrhythmias.

In a large controlled trial in patients with a recent myocardial infarction without heart failure, who did not necessarily have ventricular arrhythmias, oral sotalol HCl treatment was associated with a non-statistically significant risk reduction in mortality compared to the placebo group (18%). In this post-infarction study using a fixed dose of 320 mg once daily and in a second small randomised trial in high-risk post-infarction patients with left ventricular ejection fractions $\leq 40\%$ treated with high doses (640 mg/day), there were suggestions of an excess of early sudden deaths.

Abrupt withdrawal

Care should be taken if beta-blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of beta-blockade in patients with ischaemic heart disease. Therefore, it is recommended that the dosage be reduced gradually over a period of 8-14 days during which time the patient's progress should be assessed. Sotalol hydrochloride should be temporarily reinstated if the angina worsens. If the drug must be withdrawn abruptly in these patients, close observation is required, since latent coronary insufficiency may be unmasked. In the peri-operative period sotalol hydrochloride should not be withdrawn, unless indicated.

Concomitant therapy with 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 because of the additive effect on atrioventricular conduction and ventricular function.

Peripheral circulation

Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease.

Antiarrhythmic drugs

Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and propafenone; the Class III agent, amiodarone, and the Class IV antiarrhythmic agents. Concomitant use of sotalol hydrochloride with these agents, and with other beta blocking drugs, is not recommended.

Prinzmetal angina

There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a beta-blocker. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Euthyroid hyperthyroxinaemia

The effects of beta-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T_4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

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 and the peri-operative period

Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported.

Modern inhalational anaesthetic agents are generally well tolerated, although older agents (ether, cyclopropane, methoxyflurane, trichloroethylene) were sometimes associated with severe circulatory depression in the presence of beta-blockade.

Diabetes

Beta-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia.

In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, beta-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need to be adjusted.

Other metabolic effects

Beta adrenoreceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some drugs affect the lipid profile adversely although the long-term clinical significance of this change is unknown and the effect appears to be less for drugs with intrinsic sympathomimetic activity.

Hepatic impairment

Since sotalol hydrochloride is not subject to first pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol hydrochloride.

Renal disease

In patients with severe renal disease, haemodynamic changes following beta-blockade may impair renal function further. Beta-blockers, which are excreted mainly by the kidney, may require dose adjustment in patients with renal impairment. Sotalol excretion is reduced in patients with renal impairment. Dosage should therefore be adjusted accordingly. Sotalol is contraindicated in patients with severe renal impairment ($\text{CrCl} < 10 \text{ mL/min}$).

Use of catecholamine-depleting agents

Concomitant use of drugs such as reserpine and guanethidine requires careful monitoring since the added effect of a beta-blocker may produce an excessive reduction of the resting sympathetic nervous tone.

Clonidine

Concurrent use of beta-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker.

Phaeochromocytoma

In patients with this condition, an alpha-blocking drug (e.g. phentolamine/phenoxybenzamine) should be administered before the beta-blocker to avoid exacerbation of hypertension.

Eye and skin reactions

Various skin rashes and conjunctival xerosis have been reported with beta-blocking agents. Cross-reactions may occur between beta-blockers, therefore substitutions within the group may not necessarily preclude occurrence of symptoms.

Allergic conditions

Allergic reactions may be exaggerated by beta-blockade (e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). Beta-blockers should be avoided if there is a risk of bronchospasm.

Hyperthyroidism

Because beta-blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid status, special care should be exercised in hyperthyroid patients who are also receiving beta-blockers.

Abrupt withdrawal of beta-blockade in hyperthyroid patients may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm, and should be avoided in these patients.

Electrocardiographic monitoring

Regular electrocardiographic monitoring should be carried out during sotalol therapy because of prolongation of the QT interval (see section 4.4). Excessive prolongation of the QT interval, >550 msec, can be a sign of toxicity, and should be avoided. Sinus bradycardia (heart rate less than 50 bpm) occurred at a frequency of 13% in arrhythmia patients receiving sotalol hydrochloride in clinical trials. Bradycardia itself 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%.

Electrolyte disturbances

Prior to starting treatment with sotalol hydrochloride, serum electrolytes should be obtained and any electrolyte imbalance corrected. Hypokalaemia and hypomagnesaemia can exaggerate the degree of QT prolongation, and increase the potential for torsade de pointes. Throughout treatment it is important to monitor electrolyte balance at regular intervals and correct any imbalance. When significant diarrhoea or other intercurrent illness associated with electrolyte losses occurs during treatment with sotalol hydrochloride, patients should be instructed to contact their doctors so that they can be closely monitored with frequent checks of plasma electrolytes and receive replacement therapy as appropriate (see section 4.4).

Excessive bradycardia

If excessive bradycardia occurs alone or with hypotension, atropine 0.5 to 2.0 mg should be given intravenously and immediately followed, if necessary, by a beta receptor stimulating agent such as isoprenaline (see section 4.9).

Patients experiencing this effect on initial administration of sotalol hydrochloride should be removed temporarily from therapy. Sotalol hydrochloride may be later reintroduced at a lower dosage level.

A reduction in dosage by 80 or 160 mg/day may be advisable to alleviate symptoms of weakness and dizziness in cases where the blood pressure continues to fall after a month or two of sotalol hydrochloride administration.

Psoriasis

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

Paediatric use

The safety and effectiveness of sotalol hydrochloride in children under 18 has not been established.

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 pheochromocytoma and who are treated with sotalol should have their urine screened utilising the high performance liquid chromatographic assay with solid phase extraction.

4.5 Interaction with other medicines and other forms of interaction

Alcohol

The plasma clearance of sotalol is reduced after alcohol ingestion.

Insulin and oral hypoglycaemics

Beta-blocking drugs may prolong the hypoglycaemic action of these drugs especially in conditions where glucose mobilisation may be compromised, e.g. labile diabetes, diabetic ketoacidosis and fasting diabetic patients. Symptoms of hypoglycaemia may be masked by sotalol hydrochloride. Hyperglycaemia may occur, and the dosage of antidiabetic drugs may require adjustment (see section 4.4).

Anaesthetics

Agents such as ether, chloroform and cyclopropane are contraindicated with sotalol hydrochloride (see section 4.4).

Beta-2 receptor stimulants

Beta agonists such as salbutamol, terbutaline and isoprenaline may have to be administered in increased dosages when used concomitantly with sotalol hydrochloride.

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 because of the additive effects on atrioventricular conduction, and ventricular function (see section 4.4).

Catecholamine-depleting agents

Concomitant use of catecholamine-depleting agents, such as reserpine and guanethidine, 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.

Clonidine

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

An antagonistic effect between clonidine and sotalol has been observed. Concurrent administration of clonidine and sotalol has caused increased blood pressure compared with clonidine or sotalol alone. The combination of beta-adrenoreceptor antagonists and clonidine should be avoided (see section 4.4).

Drugs prolonging the QT interval

Drugs known to prolong the QT interval and/or to be associated with atypical ventricular tachycardia (AVT, torsade de pointes) especially quinidine, disopyramide and tricyclic antidepressants, terfenadine, astemizole and certain quinolone antibiotics should be avoided (see section 4.4).

Antiarrhythmic agents

Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and propafenone; the Class III agent, amiodarone; and the Class IV antiarrhythmic agents. Concomitant use of sotalol hydrochloride with these agents, and with other beta-blocking drugs is not recommended.

Potassium depleting diuretics

Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsade de pointes (see section 4.4).

Digoxin

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 digoxin; however, this may be related to the presence of congestive heart failure, a known risk factor for proarrhythmia, in the patient receiving digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Beta-blockers may cause bradycardia in the foetus and newborn infant. Sotalol has been shown to cross the placental barrier and cause bradycardia in the newborn.

During the late stages of pregnancy these drugs should only be given after weighing the needs of the mother against the risk to the foetus.

Breast-feeding

Sotalol is actively excreted in breast milk (milk/plasma ratio = 5.4/1) and therefore should not be administered to nursing mothers.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness, and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8 Undesirable effects

Sotalol hydrochloride is well tolerated in the majority of patients, with the most frequent adverse events arising from its beta blockade properties. Adverse events 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, these side effects usually disappear when the dosage is reduced. The most significant adverse events, however, are those due to proarrhythmia, including torsades de pointes.

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 torsades 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)
Torsades de pointes	4.1%	1.0%	1.4%
Sustained VT/VF	1.2%	0.7%	0.3%

VT = ventricular tachycardia;

VF = ventricular fibrillation;

NSVT = nonsustained ventricular tachycardia;

PVC = premature ventricular 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 were: fatigue 4%, bradycardia (< 50 bpm) 3%, dyspnoea 3%, proarrhythmia 2%, asthenia 2% and dizziness 2%.

More Common Reactions > 1%

Biochemical abnormalities

Changes in plasma lipid concentrations (see section 4.4).

Cardiovascular

Ventricular tachyarrhythmias, torsade de pointes, cold extremities, bradycardia, dyspnoea, chest pain, palpitations, oedema, ECG abnormalities, hypotension, proarrhythmia, syncope, heart failure, presyncope.

Dermatologic

Rash.

Gastrointestinal

Nausea/vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence.

Nervous system

Dizziness, drowsiness, lethargy, weakness, vertigo, lightheadedness, headache, sleep disturbances, depression, paraesthesia, mood changes, anxiety.

Urogenital

Sexual dysfunction.

Special senses

Visual disturbances (including eye irritation, deterioration of eyesight, blurred vision, photophobia), taste abnormalities, hearing disturbances.

General

Headache, tiredness, fever.

Musculoskeletal

Cramps.

Respiratory

Shortness of breath.

Less Common Reactions < 1%

Biochemical abnormalities

Changes in antinuclear factor (ANF) titres have been reported but the clinical significance of this is not clear.

Cardiovascular

Congestive heart failure, prolonged QT interval. Increased ventricular ectopic beat frequency, cardiogenic shock and AV block (I) have been observed after intravenous administration.

Dermatological

Cutaneous thickening, pruritus.

Psychiatric

Unusual dreams.

Others

Retroperitoneal fibrosis, facial atrophy.

Serious or life-threatening Reactions

Myocardial insufficiency may require treatment with digitalis and diuretics. Bradycardia may respond to atropine (see section 4.4). Bronchospasm may be reversed with a beta-2 stimulant. Hypotension, if severe, may require use of a vasopressor. Cardiac infarction following too abrupt a withdrawal of the beta-blocker from patients with ischaemic heart disease can be avoided by gradual reduction of dose. Temporary overdrive pacing is suggested as treatment of ventricular arrhythmias in association with prolonged QT interval.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Several cases, one fatal, of sotalol intoxication have been reported. Clinical features include: asystole, severe bradycardia, congestive heart failure, hypotension, prolongation of QT interval, premature ventricular complexes, ventricular tachyarrhythmias, torsades de pointes, hypoglycaemia and bronchospasm.

Close monitoring of the electrocardiogram in patients with suspected sotalol intoxication is recommended. Every effort should be made to correct promptly metabolic and electrolyte imbalances which might contribute to the initiation of ventricular arrhythmias.

Gastric lavage, and activated charcoal should be administered when an overdose of sotalol hydrochloride tablets is suspected. Bradycardia and hypotension should be corrected prior to gastric lavage or endotracheal intubation as these procedures may increase vagal tone.

Depending on the symptoms, the following therapeutic measures are suggested:

Severe bradycardia

Atropine 1 – 2 mg intravenously may be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline may be given. An appropriate regime would be 5 micrograms bolus,

followed by an infusion of 0.5 to 10 micrograms per minute, titrated to achieve the desired effect. In refractory cases the use of a cardiac pacemaker should be considered.

Heart block (second and third degree)

Transvenous cardiac pacing.

Hypotension

Severe hypotension should respond to a sympathomimetic amine, such as epinephrine, rather than isoproterenol, or norepinephrine. In refractory cases, the use of glucagon hydrochloride should be considered.

Torsade de pointes

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

Dialysis

Dialysis lowers the plasma sotalol hydrochloride concentration by approximately 20%.

Bronchospasm

A beta-2 agonist and/or aminophylline.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 *Pharmacodynamic properties*

Pharmacotherapeutic group: Beta blocking ages, non-selective, ATC code: C07AA07.

Mechanism of action

Sotalol is a non-selective beta-adrenergic receptor blocker without sympathomimetic activity or membrane stabilising activity. It causes a decrease in heart rate and a limited reduction in the force of contraction of the heart. There is a reduction in cardiac work and in myocardial oxygen demand. Sotalol does not decrease blood pressure in normotensive subjects.

Sotalol also possesses class III antiarrhythmic activity. Sotalol has no known effect on the upstroke velocity of the action potential, therefore no known effect on the depolarisation phase. Its major effects are prolongation of the atrial, ventricular and accessory pathway effective refractory periods. The effect on the ventricular myocardium may be reflected by a lengthening of the QTc interval on electrocardiographic recordings.

Like most other beta-blockers, sotalol inhibits renin release. This suppressive effect is significant both at rest and during exercise.

Clinical trials

The Electrophysiologic Study Versus Electrographic Monitoring (ESVEM) Trial was designed to compare the choice of antiarrhythmic therapy (sotalol, procainamide, quinidine, mexiletine, propafenone, imipramine and pirmenol) by programmed electrical stimulation (PES) suppression versus Holter monitor selection in patients with a history of sustained ventricular tachycardia (VT)/ventricular fibrillation (VF) whose VT/VF were also inducible by PES and PVC's of ≥ 10 beats/hour documented by Holter monitoring. Overall acute response, limited to first randomised drug, was 39% for sotalol and 30% for the pooled other drugs. Acute response rate for first drug randomised using suppression of PES induction was 36% for sotalol versus a mean of 13% for the pooled other drugs. Using the Holter monitoring endpoint, sotalol yielded 41% response versus 45%

for the other drugs combined. Among responders placed on long term therapy identified acutely as effective, sotalol, when compared to the pool of other drugs, had the lowest two-year mortality (13% versus 22%), the lowest two-year VT recurrence rate (30% versus 60%) and the lowest withdrawal rate (38% versus 75-80%). The most commonly used doses of sotalol were 320-480 mg/day (66% of patients), with 16% receiving \leq 240 mg/day and 18% receiving \geq 640 mg/day.

5.2 Pharmacokinetic properties

Absorption

Sotalol is well absorbed from the gastrointestinal tract. Peak plasma concentrations of 1.4 to 1.7 mg/L are reached at 2-3 hours after a 160 mg oral dose.

Distribution

Total apparent volume of distribution of sotalol ranges from 1.6 to 2.4 L/kg. The volume of distribution at steady state is approximately halved in the elderly.

Biotransformation

Sotalol is not metabolised by the liver and does not undergo biotransformation (no first-pass effect). There is a positive correlation between sotalol dose and plasma concentration.

Elimination

Sotalol is excreted by glomerular filtration and to a small degree by tubular secretion. After oral administration, about 75% of the dose is excreted in the urine within 72 hours as unchanged sotalol. Less than 10% is excreted in the faeces. The mean elimination half-life of sotalol is 12.7 ± 1.6 (SE) hours.

Protein binding

Sotalol does not bind to plasma proteins and does not significantly cross the blood/brain barrier. However, it is excreted in breast milk and may cross the placental barrier.

Bioavailability

The absolute bioavailability on oral administration is close to 100%. The bioavailability is decreased when sotalol hydrochloride is administered with food, especially milk.

Clinical implications of pharmacokinetic data

As sotalol is primarily excreted by the kidneys, dosage adjustment is necessary in patients with moderate renal impairment. Severe renal impairment ($\text{CrCl} < 10$ mL/min) is a contraindication.

6. Pharmaceutical Particulars

6.1 List of excipients

Both SOTALOL 80 mg and SOTALOL 160 mg tablets also contain:

- calcium hydrogen phosphate anhydrous
- maize starch
- povidone
- sodium starch glycollate
- purified talc
- magnesium stearate

SOTALOL tablets are gluten and lactose free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

SOTALOL 80 mg: Al/PE/PVdc blister. Pack size of 60 tablets.

HDPE bottle with PP lid. Pack sizes of 100 tablets or 500 tablets.

SOTALOL 160 mg: Al/PE/PVdc blister. Pack size of 60 tablets.

HDPE bottle with PP child resistant closure. Pack size of 100 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

11 November 1993

10. Date of Revision of the Text

02 May 2019

Summary table of changes

Section	Summary of new information
-	Minor editorial changes
4.3	Amended to include history of bronchospasm