

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.

Adults

Patients with a history of myocardial infarction or severe heart failure should be monitored particularly closely in the titration phase with this antiarrhythmic agent. 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. In patients with myocardial infarction and/or cardiac arrhythmias or who have been receiving long-term therapy, the medication should be gradually tapered off since abrupt discontinuation can have a detrimental effect on the clinical condition.

Severe symptomatic ventricular tachycardia

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 mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, particularly proarrhythmias.

Symptomatic supraventricular tachycardia requiring treatment

The initial dose is 80 mg of sotalol hydrochloride twice daily. If the dose is well-tolerated but insufficiently effective, the dose can be increased to 80 mg sotalol hydrochloride three times daily. This dose should not be exceeded in patients with paroxysmal atrial fibrillation.

In patients with chronic atrial fibrillation, the dose may be increased by not more than 160 mg of sotalol hydrochloride if the initial dose was not sufficiently effective but well-tolerated.

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

Special populations

Paediatric population

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

Elderly population

A potential restriction in kidney function should be considered when treating elderly patients.

Renal impairment

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

Since sotalol hydrochloride may accumulate upon repeated administration in patients with impaired renal function, the dose should be adjusted to their renal clearance capacity while monitoring heart rate (not less than 50 beats per minute) and clinical response. Sotalol hydrochloride should only be given to patients with severe renal failure under frequent ECG and serum level monitoring.

In patients with a creatinine clearance > 60 ml/min, sotalol should be administered every 12 hours. In patients with a creatinine clearance between 30 and 59 ml/min, sotalol should be administered every 24 hours. In patients with a creatinine clearance between 10 to 29 ml/min, sotalol should be administered every 36 to 48 hours. In patients with a creatinine clearance < 10 ml/min, the dose should be individualized.

Method of administration

The tablets should be swallowed whole.

Sotalol hydrochloride should be taken preferably 1-2 hours before meals. Sotalol hydrochloride should not be taken with meals since absorption of the active ingredient can be affected by the simultaneous ingestion of food (in particular, milk and dairy products).

Dose increases should not be attempted until the patient has been receiving treatment for at least two to three days.

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.
- Sinoatrial block
- Sick sinus syndrome
- bradycardia (less than 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).
- Congestive heart failure (NYHA classIV).
- Severe renal impairment (CrCl <10 mL/min).
- Risk factors of torsade de pointes (e.g., existing prolongation of QT interval) Congenital or acquired long QT syndromes.
- Hypokalemia
- Hypomagnesaemia
- Hypotension
- Late stages of peripheral arterial occlusive disease
- Metabolic acidosis
- Untreated pheochromocytoma.
- Hypersensitivity to sotalol hydrochloride, sulfonamides or to any of the excipients listed in section 6.1.
- Anaesthesia that produces myocardial depression.

The intravenous administration of verapamil or diltiazem calcium antagonists or other anti-arrhythmic 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

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.

Anaphylaxis

Sotalol hydrochloride's beta-blocking properties may elevate the patient's sensitivity to allergens and exacerbate the severity of anaphylactic reactions. Patients with a history of severe hypersensitivity reactions and patients who are currently undergoing desensitization therapy are at higher risk of developing severe 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 (epinephrine) used to treat the allergic reaction

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 (CrCl <10 mL/min).

Physicians should bear in mind that kidney function may be impaired in elderly patients.

Pheochromocytoma

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

Diabetes mellitus

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.

Monitoring is recommended in patients on strict fasts and diabetics whose blood sugar levels are subject to major fluctuations (masking of hypoglycaemic states).

Patients initiating treatment require close cardiac monitoring for ventricular arrhythmia in the titration phase of antiarrhythmic therapy and should only be started on the drug if emergency resuscitation equipment is available and if the possibility of monitoring is assured. Regular check-ups are necessary during treatment.

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, or thyrotoxic crisis and should be avoided in these patients.

Peripheral circulatory disorders such as Raynaud's syndrome and intermittent limping: this may lead to potentiation of symptoms, especially at the start of treatment.

Proarrhythmia

Post-marketing experience

The most dangerous adverse effect of antiarrhythmic drugs in patients with a history of myocardial infarction or poor ventricular function, 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 sotalol 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.

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.

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 torsade de pointes where 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. Trademark 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 torsade de pointes, however, caution should be exercised regardless of the QTc-interval.

Psoriasis

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

Abrupt withdrawal

Hypersensitivity to catecholamines is observed in patients withdrawn from beta-blocker therapy. 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 addition, hypertension may develop. In the peri-operative period sotalol hydrochloride should not be withdrawn, unless indicated.

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.

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).

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%.

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 (T₄) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Anaesthesia and the peri-operative period

As with other beta-blocking agents, Sotalol should be used with caution in patients undergoing surgery and in association with anaesthetics. . 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.

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.

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.

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.

Paediatric population

The safety and efficacy of sotalol hydrochloride has not been established in children and adolescents up to 18 years.

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, especially in association with physical exertion. 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 such as verapamil and diltiazem 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.

Noradrenaline, Clonidine and MAO inhibitors

An antagonistic effect between noradrenaline or MAO inhibitors or abrupt discontinuation of concomitant clonidine and sotalol may cause increased blood pressure. The combination of beta-adrenoreceptor antagonists and clonidine should be avoided (see section 4.4).

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.

Drugs prolonging the QT interval

Concomitant use of sotalol hydrochloride and drugs likely to prolong the QT interval such as tricyclic or tetracyclic antidepressants (imipramine, maprotiline), antihistamines (astemizole, terfenadine), quinolone antibiotics (e.g. sparfloxacin) macrolide antibiotics (erythromycin), probucol, haloperidol, halofantrine or terodiline are 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). 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

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. Antiarrhythmic agents may give rise to excessive QT interval prolongation associated with an increased risk of ventricular arrhythmia. The concomitant use of sotalol hydrochloride with other medicines possessing beta receptor-blocking properties, may lead to cumulative class II effects (reduction in blood pressure and heart rate). 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).

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 sotalol.

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. Association of digitalis glycosides with beta-blockers may increase auriculoventricular conduction time.

The negative chronotropic and dromotropic effects of sotalol hydrochloride may be enhanced by concomitant use of reserpine, clonidine, alpha-methyldopa, guanfacine or cardiac glycosides

Neuromuscular blocking agents such as tubocurarine:

Tubocurarine-induced neuromuscular blockade may be potentiated by the beta-blocking effect of sotalol hydrochloride.

4.6 Fertility, pregnancy and lactation

Pregnancy

Given the lack of experience to date regarding the use of this medicine in pregnancy, sotalol hydrochloride must only be administered during pregnancy after carefully weighing the benefit-risk ratio. The medicinal product diffuses through the placenta and reaches pharmacologically active concentrations in the foetus. Hence, bradycardia, hypotension and hypoglycaemia may occur in the foetus or new-born infant. Treatment should therefore be discontinued 48 – 72 hours before the calculated due date. New-born infants must be carefully monitored for signs of β blockade for a corresponding length of time after birth.

Breast-feeding

A significant amount of sotalol hydrochloride is excreted in breast milk (20 % – 23 % of the maternal dose). Treatment with sotalol hydrochloride is not recommended during lactation. If sotalol hydrochloride treatment is taken during lactation, babies must be monitored for signs of β blockade

Fertility

No data available.

4.7 Effects on ability to drive and use machines

This drug may affect the individual's ability to drive a vehicle, operate machinery or work safely under precarious conditions. This applies particularly at the beginning of treatment, on increasing the dose or when switching to another medication as well as when alcohol is consumed simultaneously.

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%.

Undesirable effects are assessed on the basis of the following frequencies:

Very common: ($\geq 1/10$)
 Common: ($\geq 1/100$ to $< 1/10$)
 Uncommon: ($\geq 1/1,000$ to $< 1/100$)
 Rare: ($\geq 1/10,000$ to $< 1/1,000$)
 Very rare: ($< 1/10,000$)
 Not known: (Frequency cannot be estimated on the basis of available data)

Metabolism and nutrition disorders

Common: Changes in plasma lipid concentrations (see section 4.4).
 Not known: Increase in total cholesterol and triglyceride levels, reduction in HDL cholesterol, Hypoglycemia.

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

Psychiatric disorders

Common: anxiety, confusion, sleep disturbances, mood changes, depression,
 Not known: hallucinations, unusual dreams.

Nervous system disorders

Common: syncope, presyncope, dizziness, headache, paraesthesia, taste abnormalities,

Eye disorders

Common: Visual disturbances (including eye irritation, deterioration of eyesight, photophobia),
 Not known: blurred vision, conjunctivitis, eratoconjunctivitis, reduced lacrimation (particularly in wearers of contact lenses).

Cardiac disorders

Common: torsade de pointes, arrhythmia, chest pain, exacerbation of heart failure, bradycardia, palpitations, AV conduction disorder, ventricular tachycardia, exacerbation in angina pectoris, prolonged QT interval.

Not known: Congestive heart failure, Increased ventricular ectopic beat frequency, cardiogenic shock and AV block (I) have been observed after intravenous administration.

Vascular disorders

Common: Exacerbation of peripheral occlusive disease, cold limbs. (cold extremities),

Respiratory, thoracic and mediastinal disorders

Common: Shortness of breath, dyspnoea,

Gastrointestinal disorders

Common: abdominal pain, nausea, vomiting, diarrhoea, dyspepsia, flatulence.

Not known: Dry mouth.

Skin and subcutaneous tissue disorders

Common: skin reactions.

Not known: Drugs with beta-blocking activity may trigger psoriasis, exacerbate this condition or give rise to psoriatic exanthema. Cutaneous thickening, pruritus.

Musculoskeletal and connective tissue disorders

Common: Muscle spasms.

Reproductive system and breast disorders

Common: Impotence.

Ear and labyrinth disorders

Common: hearing disturbances.

General disorders

Common: Exacerbation of weakness, fever, fatigue, oedema, drowsiness, lethargy, vertigo, lightheadedness, headache, tiredness,

Not known: Retroperitoneal fibrosis, facial atrophy.

Investigations

Common: Blood pressure decreased (hypotension), ECG abnormalities,

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

Intentional or accidental overdosage with sotalol has rarely resulted in death.

Symptoms

The most common signs to be expected are asystole, severe bradycardia, congestive heart failure, hypotension, bronchospasm and Hypoglycaemia.

In cases of massive intentional overdose (2 – 16g) of sotalol the following clinical findings were seen: hypotension, bradycardia, prolongation of QT interval, premature ventricular complexes, ventricular tachyarrhythmias, torsades de pointes,

If overdosage occurs, therapy with sotalol should be discontinued and the patient observed closely.

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.

Treatments

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

Severe bradycardia

Atropine 0.5 to 2 mg intravenously may be used to induce vagal blockade. If bradycardia persists, another anticholinergic drug, a beta-adrenergic agonist may be given intravenously (isoprenaline 5 micrograms per minute up to 25 micrograms per minute, by slow IV injection) titrated to achieve the desired effect. In refractory cases the use of a transvenous 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 depending on associated factors. 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 results in a large reduction of plasma levels of sotalol hydrochloride concentration by approximately 20%.

Bronchospasm

An aerosol beta-2 agonist stimulant 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: class III anti-arrhythmic with marked Beta receptor blockade,

ATC code: C07AA07.

Mechanism of action

Sotalol is a non-selective beta-adrenergic receptor blocker without intrinsic sympathomimetic activity or membrane stabilising activity and low lipid solubility. Among beta blockers, it uniquely

possesses both class II and class III antiarrhythmic characteristics. 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.

D, L -sotalol is a hydrophilic class III antiarrhythmic agent with marked beta adrenergic blocking activity. 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 bundles and ventricles, lengthening the effective refractory periods. These affect the terminal phase of the monophasic action potential without affecting the conduction time. 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. The beta-adrenergic blocking effect, without intrinsic sympathomimetic activity, associated with the levorotatory isomer blocks both the β_1 and β_2 receptors equally. Depending on the tone of the sympathetic nervous system, the substance reduces heart rate, myocardial contractility, plasma renin activity, and increases AV conduction time. Smooth muscle tone may be increased as a result of its inhibitory effect on β_2 receptors.

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 pirlmenol) 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 ≤ 240 mg/day and 18% receiving ≥ 640 mg/day.

5.2 Pharmacokinetic properties

Absorption

Sotalol is well absorbed from the gastrointestinal tract (75 to 90%). Due to the absence of a first pass effect, the absolute bioavailability lies between 75 and 90%.

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. There is no plasma protein binding.

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. No pharmacologically active metabolites have been detected so far.

Elimination

Sotalol is exclusively excreted by the kidney. It is excreted by glomerular filtration and to a small degree by tubular secretion. Renal clearance is 120 ml/minute and corresponds to total body clearance. 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.

The plasma half-life is about 15 hours. This, however, can be prolonged up to 42 hours in cases of end-stage renal failure. Peak plasma levels are reached at two to three hours after oral dosing.

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 (CrCl <10 mL/min) is a contraindication.

5.3 Preclinical safety data

Preclinical data based on conventional studies of safety pharmacology, chronic toxicity, genotoxicity and carcinogenic potential show no specific risks to humans.

Reproduction toxicological studies conducted in rats and rabbits have not highlighted any teratogenic effects of sotalol hydrochloride. Low birth weights have been observed in rats and rabbits as well as altered receptor densities in the brain and changes in behavioural patterns in rats.

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
Customer Services Freephone: 0800 579 811

9. Date of First Approval

11 November 1993

10. Date of Revision of the Text

27 October 2020

Summary table of changes

Section	Summary of new information
4.2, 4.4, 4.5, 4.8, 4.9, 6.1, 6.2	Minor editorial changes Including rearrangement of sections
4.2	Reduce highest daily dose to 480 mg/day. Addition of monitoring information. Addition of gradual withdrawal statement for patients on long-term therapy. Addition of dosage information for symptomatic supraventricular tachycardia requiring treatment. Statement on consideration of dose for elderly. More information on treating patients with renal impairment. Statement to swallow tablets whole. More information on amount of time before a meal the tablets should be taken. Statement on dose increases only after patient has been receiving treatment for at least two to three days.

Section	Summary of new information
4.3	Additional contraindications included. Addition of statement for drugs used on intensive care patients.
4.4	Added statement to anesthesia and the peri-operative period section More information on anaphylaxis, renal disease, hyperthyroidism, proarrhythmia, psoriasis and abrupt withdrawal Addition of information on: Pheochromocytoma, diabetes mellitus and paediatric population. Removal of some information for proarrhythmia as new/additional information added.
4.5	More information added for: Insulin and oral hypoglycaemics, calcium channel blocking drugs, noradrenaline, Clonidine and MAO inhibitors, drugs prolonging the QT interval, antiarrhythmic agents, potassium-depleting drugs, digoxin and neuromuscular blocking agents such as tubocurarine.
4.6	Updated information on pregnancy and breast feeding.
4.7	Additional information added to Effects on ability to drive and use machines.
4.8	System organ classification headings updated. Additional side effects added.
4.9	Additional information added on some symptoms. Symptoms and treatments headings added. Additional information added for some treatments. Updated information for some treatments.
5.1	Additional information on: Pharmacotherapeutic group and mechanism of action
5.2	Additional information for absorption, distribution, biotransformation and elimination.
5.3	Preclinical safety data section added.
8	Sponsor phone number updated.
10	Updated date of preparation.