AUSTRALIAN PRODUCT INFORMATION
CARDOL® (SOTALOL HYDROCHLORIDE)

1. NAME OF THE MEDICINE

Sotalol hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of sotalol as the active ingredient.

Excipients with known effect: sugars as lactose

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

CARDOL 80 mg tablet: White, round tablets, scored on one side, convex with "SOT" embossed on the other.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Prevention and treatment of supraventricular and ventricular arrhythmias.

4.2. DOSE AND METHOD OF ADMINISTRATION

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

As with other antiarrhythmic agents, sotalol 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.

Sotalol tablets should be taken preferably one to two hours before meals.

Oral dosage of sotalol 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 twelve 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 to 320 mg/day, given in two divided doses. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480 to 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, dosing on more than a twice daily regimen is not usually necessary.

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

4.3. CONTRAINDICATIONS

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 to 50 beats/minute).

Second and third degree atrioventricular block or sick sinus syndrome unless a functioning pacemaker is present.

Shock (including cardiogenic and hypovolaemic shock).

Uncontrolled congestive heart failure.

Severe renal impairment (creatinine clearance < 10 mL/minute).

Congenital or acquired long QT syndromes.

Hypersensitivity to sotalol hydrochloride, other beta blockers, sulfonamides or the excipients.

Anaesthesia that produces myocardial depression.

Severe sinus node dysfunction.

Sinoatrial block.

Hypomagnesaemia.

Hypotension.

Late stages of peripheral arterial occlusive disease.

Metabolic acidosis.

Torsades de pointes.

Raynaud's phenomenon and severe peripheral circulatory disturbance.

Untreated phaeochromocytoma.

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).

Hypokalaemia.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with supraventricular or asymptomatic ventricular arrhythmias

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.

Mortality:

Post-myocardial infarction patients with asymptomatic ventricular arrhythmias showed a significant increase in mortality and in non-fatal cardiac arrest rate in patients treated with encainide or flecainide compared with a matched placebo-treated group. The Cardiac Arrhythmia Suppression Trial (CAST) was continued using a revised protocol with the moricizine and placebo arms only. The trial was prematurely terminated because of a trend towards an increase in mortality in the moricizine treated group. The applicability of these results to other populations or other antiarrhythmic agents is uncertain, but at present it is prudent to consider these results when using any antiarrhythmic agent.

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 concentrations (e.g. as a consequence of overdosage or renal insufficiency), and with the concomitant use of sotalol and other medication such as antidepressants and class I antiarrhythmics which have been associated with torsades de pointes. Females appear to be at an 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 in patients whose pretreatment QTc interval exceeded 450 milliseconds. Sotalol 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 (e.g. syncope), they can progress to ventricular fibrillation.

Clinical studies for Arrhythmia. During clinical trials, 4.3% of 3,257 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 in Table 1.

Table 1. Percentage incidence of serious proarrhythmias* by dose for patients with sustained ventricular tachycardia or ventricular fibrillation

Daily dose of sotalol (mg)	Incidence of serious Proarrhythmias	Number of Patients
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 ventricular tachycardia or fibrillation

In clinical trials of patients with sustained VT/VF the incidence of severe proarrhythmia (torsades de pointes or new sustained VT/VF) was <2% at doses up to 320 mg. The incidence more than doubled at higher doses.

Other risk factors for torsades de pointes were excessive prolongation of the 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 (approximately 7%). Proarrhythmic events must be anticipated not only on initiating therapy but with every upward dose adjustment; events tend to occur within seven 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 proarrhythmic events (see Section 4.2 Dose and method of administration). Sotalol should be used with caution if the QTc interval is greater than 500 milliseconds on therapy, and serious consideration should be given to reducing the dose or discontinuing therapy when the QT interval exceeds 550 milliseconds. Due to the multiple risk factors associated with torsades de pointes, however, caution should be exercised regardless of the QTc interval.

Proarrhythmic events must be anticipated not only on initiating therapy, but with every upward dose adjustment. Proarrhythmic events most often occur within 7 days of initiating therapy or of an increase in dose; a large percentage of serious proarrhythmias (torsade de pointes and worsened VT) occurred within 7 days of initiating sotalol therapy, while the majority of such events occurred within 3 days of initiation or a dosage change. Initiating therapy at 80 mg BID with gradual upward dose titration and appropriate evaluations for efficacy (e.g. PES or Holter) and safety (e.g. QT interval, heart rate and electrolytes) prior to dose escalation, should reduce the risk of proarrhythmia. Avoiding excessive accumulation of sotalol in patients with diminished renal function, by appropriate dose reduction, should also reduce the risk of proarrhythmia (see Section 4.2 Dose and method of administration).

Congestive heart failure

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure (CHF), and 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. Moreover, patients with CHF have a higher risk

of torsade de pointes (see Section 4.4 Special warnings and precautions for use - Proarrhythmia). In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If cardiac failure persists, sotalol should be discontinued (see Section 4.4 Special warnings and precautions for use - Abrupt Withdrawal).

In patients with controlled CHF, sotalol should be administered cautiously. The positive inotropic action of digitalis may be reduced when the two drugs are used concomitantly. Both digitalis and sotalol slow AV conduction. If cardiac failure continues despite adequate digitalisation, sotalol should be discontinued. In patients without a history of heart failure, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. At the first sign of impending heart failure, appropriate therapy must be established and consideration should be given to discontinuation of treatment with sotalol.

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.

Conduction Disturbances

Excessive prolongation of the QT interval (> 550 msec) can promote serious arrhythmias and should be avoided (see Section 4.4 Special warnings and precautions for use - Proarrhythmia). Sinus bradycardia (heart rate less than 50 bpm) occurred in some patients receiving sotalol in clinical trials, and led to discontinuation in a small percentage of patients. Bradycardia itself increases the risk of torsade 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%.

Recent myocardial infarction

In post-infarction patients with impaired left ventricular function, the risk versus benefit of sotalol administration must be considered. Careful monitoring and dose titration are critical during initiation and follow-up of therapy. The adverse results of clinical trials involving antiarrhythmic drugs (i.e. apparent increase in mortality) suggest that sotalol 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 hydrochloride treatment was associated with a risk reduction in mortality that was not statistically significant 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. Hypersensitivity to catecholamines is observed in patients withdrawn from beta

blocker therapy. Severe exacerbation of angina pectoris and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of beta-blockade in patients with ischaemic heart disease. In addition, hypertension may develop. Therefore, it is recommended that the dosage be reduced gradually over a period of 8 to 14 days during which time the patient's progress should be assessed. Sotalol should be temporarily reinstituted 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 should not be withdrawn unless indicated.

Non-Allergic Bronchospasm (e.g., chronic bronchitis and emphysema)

Patients with bronchospastic diseases should in general not receive beta-blockers. It is prudent, if sotalol is to be administered, to use the smallest effective dose, so that inhibition of bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta-2 receptors may be minimised.

Sick Sinus Syndrome

Sotalol should be used only with extreme caution in patients with sick sinus syndrome associated with symptomatic arrhythmias, because it may cause sinus bradycardia, sinus pauses or sinus arrest.

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 and circulatory disorders (such as Raynaud's syndrome and intermittent limping), especially at the start of treatment.

Antiarrhythmic drugs

Interactions have been reported during concomitant beta-blocker therapy with the class IA agents disopyramide and, less frequently, quinidine; the class IB agents tocainide, mexiletine and lidocaine (lignocaine); the class IC agents flecainide and propafenone (not available in Australia); the class III agent amiodarone; and the class IV antiarrhythmic agents. Concomitant use of sotalol 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 elevation 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

Sotalol's beta-blocking properties may elevate the patient's sensitivity to allergens and exacerbate the severity of anaphylactic reactions. There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. Patients with a history of severe hypersensitivity reactions and patients who are currently undergoing desensitisation therapy are at higher risk of developing severe anaphylactic reactions. Sotalol should therefore only be administered to such patients if absolutely indicated. Patients with a history of anaphylactic reaction to a variety of allergens may have more severe reaction on repeated challenge while taking beta-blockers. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reaction. Adrenaline (epinephrine) should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of adrenaline (epinephrine) may be needed to overcome the bronchospasm, while on the other hand, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia, and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of adrenaline (epinephrine) include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Anaesthesia and the perioperative period

Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the postoperative period. It is currently recommended that maintenance beta-blockade be continued perioperatively. 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. Sotalol should be used with caution in patients undergoing surgery.

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

Diabetes

Sotalol should be used with caution in patients with diabetes (especially labile diabetes) because 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.

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.

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.

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, 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 honey 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 Special warnings and precautions for use - Proarrhythmia, Post-Marketing Experience). Excessive prolongation of the QT interval (>550

milliseconds) can be a sign of toxicity and should be avoided. Sinus bradycardia (heart rate < 50 beats/minute) occurred at a frequency of 13% in arrhythmia patients receiving sotalol 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 second or third degree atrioventricular block is approximately 1%.

Electrolyte disturbances

Sotalol 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.

Prior to starting treatment with sotalol, serum electrolytes should be obtained and any electrolyte imbalance corrected. It is important to monitor electrolyte balance at regular intervals and correct any imbalance throughout therapy. When significant diarrhoea or other intercurrent illness associated with electrolyte losses occurs during treatment with sotalol, patients should be instructed to contact their physicians so that they can be closely monitored with frequent checks of plasma electrolytes and receive replacement therapy as appropriate (see Section 4.4 Special warnings and precautions for use - Proarrhythmia, Post-Marketing Experience).

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 Overdose).

Patients experiencing this effect on initial administration of sotalol should be removed temporarily from therapy. Sotalol 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 administration.

Psoriasis

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

Pheochromocytoma

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

Use in Hepatic Impairment

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

Use in Renal Impairment

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 (creatinine clearance < 10mL/minute).

Use in the Elderly

No data available.

Paediatric Use

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

Effects on Laboratory Tests

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 utilising the high performance liquid chromatographic assay with solid phase extraction.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Alcohol

The plasma clearance of sotalol is reduced after alcohol ingestion.

Insulin and oral hypoglycaemics

Concomitant use of sotalol hydrochloride and insulin or oral antidiabetic agents may induce hypoglycaemia. 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. Hyperglycaemia may occur and the dosage of antidiabetic drugs may require adjustment (see Section 4.4 Special warnings and precautions for use - Diabetes).

Anaesthetics

Agents such as ether, chloroform and cyclopropane are contraindicated with sotalol (see Section 4.4 Special warnings and precautions for use - Anaesthesia and the Peri-operative period).

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.

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 Special warnings and precautions for use - Concomitant therapy with Calcium Channel Blocking Drugs).

Catecholamine depleting agents

Concomitant use of catecholamine depleting drugs, e.g. reserpine and 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.

Noradrenaline, Clonidine and MAO inhibitors

An antagonistic effect between noradrenaline or MAO inhibitors or abrupt discontinuation of concomitant 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 Special warnings and precautions for use - 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.

Drugs prolonging the QT interval

Drugs known to prolong the QT interval and/or to be associated with atypical ventricular tachycardia (AVT, torsades de pointes), especially phenothiazines, quinidine, disopyramide, tricyclic antidepressants, terfenadine, astemizole, and certain quinolone antibiotics (e.g. sparfloxacin) macrolide antibiotics (erythromycin), probucol, haloperidol, halofantrine or terodiline should be avoided (see Section 4.4 Special warnings and precautions for use - Proarrhythmia, Post-Marketing Experience).

Other drugs that have been associated with an increased risk for torsades de pointes include erythromycin IV, halofantrine, 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 vasodilator.

Antiarrhythmic agents

Interactions have been reported during concomitant beta-blocker therapy with the class IA agents disopyramide and less frequently, quinidine; the class IB agents tocainide, mexiletine and lidocaine (lignocaine); the class IC agents flecainide and propafenone (not available in Australia); the class III agent amiodarone; and the class IV antiarrhythmic agents. Concomitant use of sotalol with these agents, and with other beta-blocking drugs, is not recommended because of their potential to prolong refractoriness. The concomitant use of other beta-blocking agents with sotalol may result in additive Class II effects.

Potassium depleting diuretics

Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsades de pointes (see Section 4.4 Special warnings and precautions for use - Electrolyte Disturbances).

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 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 auriculo-ventricular 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.

Floctafenine

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

Neuromuscular blocking agents like Tubocurarin

The neuromuscular blockade is prolonged by beta-blocking agents.

Insulin and oral hypoglycemics

Hypoglycemia and hyperglycemia may occur and the dosage of antidiabetic drug should be adjusted accordingly (See Section 4.4 Special warnings and precautions for use - Diabetes). Symptoms of hypoglycaemia (tachycardia) may be masked by beta-blocking agents.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Pregnancy Category: C

Australian Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and newborn infant. Sotalol has been shown to cross the placental barrier and cause bradycardia or hypoglycaemia in the newborn infant.

During the late stages of pregnancy these drugs should only be given after weighing the needs of the mother against the risk to the fetus. The neonate should be monitored very carefully for 48 – 72 hours after delivery if it was not possible to interrupt maternal therapy with sotalol 2-3 days before the birthdate.

Use in lactation

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

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. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Sotalol is well tolerated in the majority of patients, with the most frequent adverse events arising from its beta-blockade properties. Adverse reactions 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.

Frequency is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000) including isolated reports. The following are adverse events considered related to therapy with Sotalol:

System Organ Class	Common	Unknown
Cardiac disorders	Ventricular Tachyarrhythmias Torsade de pointes Chest pain Exacerbation of heart failure Bradycardia Hypotension Cold extremities Dyspnoea Palpitations Oedema ECG abnormalities AV conduction disorder Ventricular tachycardia Exacerbation in angina pectoris Prolonged QT interval Proarrhythmia Arrhythmia Syncope Heart failure Presyncope Hypotension and bradycardia are more frequent after intravenous administration	Congestive heart failure, Increased ventricular ectopic beat frequency, cardiogenic shock and AV block (I) have been observed after intravenous administration.
Vascular disorders	Exacerbation of peripheral occlusive disease, cold limbs (cold extremities) Vasodilation AICD discharge Hypertension	
Haematologic disorders	Bleeding	
Biochemical abnormalities	Changes in plasma lipid concentrations	
Skin and subcutaneous tissue disorder	Rash Skin reactions	Alopecia Hyperhidrosis Drugs with beta-blocking activity may trigger psoriasis, exacerbate this condition or

		give rise to psoriatic exanthema Cutaneous thickening Pruritus
Gastrointestinal disorder	Diarrhoea Nausea/vomiting Flatulence Dyspepsia Abdominal pain Colon problems	Dry mouth
Musculoskeletal, connective tissue and bone disorders	Muscle spasms Cramps Extremity pain Back pain	
Nervous system disorders	Dizziness Drowsiness Lethargy Fatigue Asthenia Weakness Vertigo Lightheadedness Headache Sleep disturbances Paraesthesia Dysgeusia Perspiration Altered consciousness Paresthesia Stroke Taste abnormalities	
Psychiatric disorders	Sleep disorder Depression Mood changes Anxiety Confusion Appetite disorder	Hallucinations
Reproductive system and breast disorders	Sexual dysfunction Impotence	
Respiratory disorders	Pulmonary problem Upper respiratory tract problem Asthma	
Metabolic and nutrition disorders	Abnormal lab value Weight change Changes in plasma lipid concentrations (see section 4.4)	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.
Eye disorders	Visual disturbances (including eye irritation, deterioration of eyesight, blurred vision, photophobia)	Conjunctivitis, keratoconjunctivitis, reduced lacrimation (particularly in wearers of contact lenses)

Ear and labyrinth disorders	Hearing disturbances	
General disorders and administration site conditions	Pyrexia Taste abnormalities Shortness of breath Exacerbation of weakness Oedema Dyspnoea Infection Localised pain	Retroperitoneal fibrosis Facial atrophy

In clinical trials, 3256 patients with cardiac arrhythmias (1,363 with sustained ventricular tachycardia) received oral sotalol, of whom 2,451 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 Special warnings and precautions for use - Proarrhythmia, Post-Marketing Experience), which occurred at rates outlined in Table 2.

Table 2. Percentage incidence of torsades de pointes and sustained ventricular tachycardia/fibrillation

	Patient population		
Adverse event	**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 were fatigue 4%, bradycardia (< 50 beats/minute) 3%, dyspnoea 3%, proarrhythmia 2%, asthenia 2% and dizziness 2%.

Cold and cyanotic extremities, Raynaud's phenomenon, increase in existing intermittent claudication and dry eyes have been seen in association with other beta-blockers.

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 first degree atrioventricular block have been observed after intravenous administration.

Dermatological. Cutaneous thickening, pruritus.

Psychiatric. Unusual dreams.

Others. Retroperitoneal fibrosis, facial atrophy.

Severe or life-threatening reactions

Myocardial insufficiency may require treatment with digitalis and diuretics. Bradycardia may respond to atropine (see Section 4.4 Special warnings and precautions for use - Excessive Bradycardia). Bronchospasm may be reversed with a beta-2stimulant. 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.

Not known: (Frequency cannot be estimated on the basis of available data)

Blood and lymphatic system disorders. Thrombocytopenia – frequency unknown.

Skin and subcutaneous tissue disorders. Alopecia, hyperhidrosis – frequency unknown.

Other potential adverse effects

Marketing experience with sotalol hydrochloride shows an adverse experience profile similar to that described above from clinical trials. Voluntary reports since introduction include rare reports (less than one report per 10,000 patients) of: emotional lability, slightly clouded sensorium, in coordination, vertigo, paralysis, thrombocytopenia, eosinophilia, leukopenia, photosensitivity reaction, fever, pulmonary oedema, hyperlipidaemia, myalgia, pruritus, reversible alopecia.

Additional adverse effects have been reported with other beta-adrenergic blocking agents.

Central Nervous System. Reversible mental depression progressing to catatonia; and acute reversible syndrome characterised by disorientation for time and place, short-term memory loss and decreased performance on neuropsychometrics.

Allergic. Fever, combined with aching and sore throat, laryngospasm, respiratory distress.

Hematologic. Agranulocytosis; thrombocytopenic or nonthrombocytopenia purpura.

Gastrointestinal. Mesenteric arterial thrombosis; ischemic colitis.

Other. Peyronie's disease, Raynaud's phenomenon

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

Symptoms

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.

Treatment

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 Cardol 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 to 2 mg intravenously may be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline may be given. An appropriate regimen would be a 5 microgram bolus followed by an infusion of 0.5 to 10 microgram/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 isoprenaline or noradrenaline. In refractory cases, the use of glucagon hydrochloride should be considered.

Torsades de pointes. DC cardioversion, transvenous cardiac pacing, adrenaline (epinephrine) and/or intravenous magnesium sulfate.

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

Bronchospasm. A beta-2-agonist and/or aminophylline.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

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 and 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 (QT interval corrected for heart rate) 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

No data available.

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 to 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.

Metabolism

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.

Excretion

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.

Bioavailability

The absolute bioavailability on oral administration is close to 100%. The bioavailability is decreased when sotalol 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 (creatinine clearance < 10 mL/minute) is a contraindication.

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.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

CARDOL tablets also contain maize starch, lactose monohydrate, hyprolose, sodium starch glycollate, colloidal anhydrous silica and magnesium stearate.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5. NATURE AND CONTENTS OF CONTAINER

Container type: PP/Al blister packs

Pack sizes: 60 tablets

Australian Register of Therapeutic Goods (ARTG)

AUST R 262936 – CARDOL sotalol hydrochloride 80mg tablet blister pack

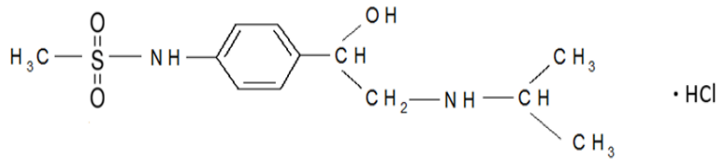
6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7. PHYSICOCHEMICAL PROPERTIES

Sotalol hydrochloride is a white crystalline solid, soluble in water (50% w/v) and has a melting point of 210°C.

Chemical structure



Chemical Name

4'-(2-isopropylamino-1-hydroxy-ethyl)-methanesulfonanilide hydrochloride

Molecular formula

$C_{12}H_{20}N_2O_3S \cdot HCl$

Molecular weight

303.83

CAS number

959-24-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Sandoz Pty Ltd
100 Pacific Highway
North Sydney, NSW 2060
Australia

Tel 1800 726 369

9. DATE OF FIRST APPROVAL

14/12/2015

10. DATE OF REVISION

20/11/2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Additional contraindications
4.4	Additional warning regarding peripheral circulation and pheochromocytoma.
4.5	Additional information regarding the interactions with 'insulin and oral hypoglycaemics' and 'digoxin'. Minor editorial changes.
4.8	Additional adverse events associated with 'Nervous system disorders', 'Psychiatric disorders', 'Eye disorders' and 'Metabolic and nutrition disorders'. Updated adverse common events associated with 'General disorders and administration site conditions'.
5.1	Minor editorial changes

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