

# NEW ZEALAND DATA SHEET

## 1 PRODUCT NAME

SOTACOR sotalol hydrochloride 80mg tablet

SOTACOR sotalol hydrochloride 160mg 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 plain on one side and engraved "BMS 621" with a bisect bar on the other side.

The 160 mg tablet is plain on one side and engraved "BMS 160" with a bisect bar on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Dose and method of administration

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

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

Oral dosage of Sotacor should be adjusted gradually allowing 2-3 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 160mg/daily, given in two divided doses at approximately 12 hour intervals. This dose may be increased, if necessary, after appropriate evaluation to 240 or 320mg/day. In most patients, a therapeutic response is obtained at a total daily

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dose of 160-320mg/day, given in 2 divided doses. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480-640mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events particularly proarrhythmias.

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

### ***Special populations***

#### **With Impaired Renal Function**

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

#### ***Method of administration***

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

### 4.3 Contraindications

1. Bronchospasm (eg bronchial asthma or chronic obstructive airway disease).
2. Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm.
3. Right ventricular failure secondary to pulmonary hypertension.
4. Significant right ventricular hypertrophy.
5. Sinus bradycardia (less than 45-50 beats/minute).
6. Second and third degree A-V block or sick sinus syndrome unless a functioning pacemaker is present.
7. Shock (including cardiogenic and hypovolaemic shock).
8. Uncontrolled congestive heart failure.
9. Sever renal impairment (CrCl< 10mL/min).
10. Congenital or acquired long QT syndromes.
11. Hypersensitivity to sotalol hydrochloride or the excipients.
12. Anesthesia that produces myocardial depression.

### 4.4 Special warnings and precautions for use

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

#### **Proarrhythmia**

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### **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 (eg, as a consequence of diuretic use), high plasma drug concentration (eg, as a consequence of overdose or renal insufficiency), and with the concomitant use of **sotalol** and other medication such as antidepressants and Class 1 antiarrhythmics which have been associated with torsades de pointes. Females appear to be at increased risk of developing torsades de pointes. EKG monitoring immediately prior to or following the episodes usually reveals a significantly prolonged QT interval and a significantly prolonged QTc interval. In clinical trials, Sotacor generally has not been initiated to patients whose pre-treatment QTc interval exceeded 450 msec. Sotacor should be titrated very cautiously in patients with prolonged QT intervals.

Torsades de pointes is dose dependent, usually occurs early after initiating therapy or escalation of the dose, and terminates spontaneously in the majority of patients. Although most episodes of torsades de pointes are self-limited or associated with symptoms (eg, syncope), they can progress to ventricular fibrillation.

### **Clinical studies for arrhythmia:**

During clinical trials, 4.3% of 3257 patients with arrhythmias experienced a new or worsened ventricular arrhythmia, including sustained ventricular tachycardia (approximately 1%) and torsades de pointes (2.4%). In addition, in approximately 1% of patients, deaths were considered possibly drug-related.

In patients with other, less serious, ventricular arrhythmias and supraventricular arrhythmias, the incidence of torsades de pointes was 1% and 1.4% respectively.

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

#### **Percent Incidence of Serious Proarrhythmias<sup>§</sup> by dose for patients with sustained VT/VF**

Daily Dose (mg)	Incidence of Serious Proarrhythmias <sup>§</sup>	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)

<sup>§</sup> 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 (≈7%).

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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 80mg twice daily with gradual upward dose titration thereafter reduces the risk of proarrhythmia (see **section 4.2**). Sotacor 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, Sotacor 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 (ie, apparent increase in mortality) suggest that Sotacor 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 postinfarction study using a fixed dose of 320mg 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 (640mg/day), there were suggestions of an excess of early sudden deaths.

### **Abrupt withdrawal**

Care should be taken if beta blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of beta-blockade in patients with ischaemic heart disease. Therefore, it is recommended that the dosage be reduced gradually over a period of 8-14 days during which time the patient's progress should be assessed. Sotacor should be temporarily reinstated if the angina worsens.

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If the drug must be withdrawn abruptly in these patients, close observation is required, since latent coronary insufficiency may be unmasked. In the perioperative period Sotacor (**sotalol hydrochloride**) should not be withdrawn, unless indicated.

### **Concomitant therapy with calcium channel blocking drugs**

Concurrent administration of beta-blocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects and cardiac failure. Beta-blockers should be avoided in combination with cardiodepressant calcium-channel blockers because of the additive effect on atrioventricular conduction and ventricular function.

### **Peripheral circulation**

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

### **Antiarrhythmic drugs**

Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lignocaine; Class IC agents, flecainide and propafenone; the Class III agent, amiodarone, and the Class IV antiarrhythmic agents. Concomitant use of Sotacor 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.

### **Anaphylaxis**

Patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge while taking betablockers. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reaction.

### **Anaesthesia and the peri-operative period**

Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the postoperative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be made aware of betablockade 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.

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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**

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

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

### **Other metabolic effects**

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

### **Hepatic Impairment**

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

### **Renal disease**

In patients with severe renal disease, haemodynamic changes following betablockade 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 <10mL/min).

### **Use of catecholamine-depleting agents**

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

### **Clonidine**

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

### **Phaeochromocytoma**

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

### **Eye and skin reactions**

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Various skin rashes and conjunctival xerosis have been reported with betablocking 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 (eg, allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). Betablockers should be avoided if there is a risk of bronchospasm.

### Hyperthyroidism

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

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

### Electrocardiographic monitoring

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

### Electrolyte disturbances

Prior to starting treatment with Sotacor, 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 Sotacor, patients should be instructed to contact their doctors so that they can be closely monitored with frequent checks of plasma electrolytes and receive replacement therapy as appropriate. (See **section 4.4**).

### Excessive bradycardia

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

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

### Psoriasis

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

### **Paediatric Use**

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

### **Drug/laboratory interaction**

The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by photometric methods. Patients suspected of having 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 Interaction with other medicines and other forms of interaction

### **Alcohol**

The plasma clearance of **sotalol** is reduced after alcohol ingestion.

### **Insulin and oral hypoglycaemics**

Beta-blocking drugs may prolong the hypoglycaemic action of these drugs especially in conditions where glucose mobilisation may be compromised, e.g., labile diabetes, diabetic ketoacidosis and fasting diabetic patients. Symptoms of hypoglycaemia may be masked by Sotacor. 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 Sotacor (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 Sotacor.

### **Calcium channel blocking drugs**

Concurrent administration of beta-blocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects and cardiac failure. Beta-blockers should be avoided in combination with cardiodepressant calcium-channel blockers because of the additive effects on atrioventricular conduction and ventricular function (see **section 4.4**).

### **Catecholamine-depleting agents**

Concomitant use of catecholamine-depleting drugs, such as reserpine and guanethidine, with a beta-blocker may produce an excessive reduction of resting sympathetic nervous tone. Patients should be closely monitored for evidence of hypotension and/or marked bradycardia which may produce syncope.

### **Clonidine**

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

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

### **Drugs prolonging the QT interval**

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

### **Antiarrhythmic agents**

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

### **Potassium-depleting diuretics**

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

### **Digoxin**

Single and multiple doses of Sotacor 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 CHF, a known risk factor for proarrhythmia, in the patient receiving digoxin.

## 4.6 Fertility, pregnancy and lactation

### **Use in Pregnancy**

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

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

### **Use in Lactation**

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

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### 4.7 Effects on ability to drive and use machines

No data available.

### 4.8 Undesirable effects

Sotacor 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 torsade de pointes.

In clinical trials, 3256 patients with cardiac arrhythmias (1363 with sustained ventricular tachycardia) received oral Sotacor, of whom 2451 received the drug for at least two weeks. The most significant adverse events were torsade de pointes and other serious new ventricular arrhythmias (see **section 4.4**), which occurred at the following rates:

Patient population			
	VT / VF	NSVT / PVC	SVA
	(n=1363)	(n=946)	(n=947)
Torsade de pointes	4.1%	1.0%	1.4%
Sustained VT / VF	1.2%	0.7%	0.3%

VT = ventricular tachycardia

VF = ventricular fibrillation

NSVT = non-sustained 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 Sotacor were: fatigue 4%, bradycardia (<50bpm) 3%, dyspnoea 3%, proarrhythmia 2%, asthenia 2% and dizziness 2%.

#### **More Common Reactions > 1%**

##### ***Biochemical abnormalities***

Changes in plasma lipid concentrations (see **section 4.4**).

##### ***Cardiovascular***

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Ventricular tachyarrhythmias, torsade de pointes, chest pain, bradycardia, hypotension, cold extremities, dyspnoea, palpitations, oedema, ECG abnormalities, proarrhythmia, syncope, heart failure, presyncope. Hypotension and bradycardia are more frequent after intravenous administration.

### ***Dermatological***

Rash.

### ***Gastrointestinal***

Diarrhoea, nausea/vomiting, flatulence, dyspepsia, abdominal pain.

### ***General***

Headache, tiredness, fever.

### ***Musculoskeletal***

Cramps

### ***Nervous system***

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

### ***Special senses***

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

### ***Urogenital***

Sexual dysfunction.

### ***Respiratory***

Shortness of breath.

### **Less Common Reactions < 1%**

#### ***Biochemical abnormalities***

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

#### ***Cardiovascular***

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

#### ***Dermatological***

Cutaneous thickening, pruritus.

#### ***Psychiatric***

Unusual dreams.

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## **Others**

Retroperitoneal fibrosis, facial atrophy.

## **Serious or Life Threatening Reactions**

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

## **Reporting of suspected adverse reactions**

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

## 4.9 Overdose

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

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

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

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

### **Severe bradycardia**

Atropine 1-2 mg intravenously may be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline may be given. An appropriate regime would be 5 micrograms bolus, followed by an infusion of 0.5 to 10 micrograms per minute, titrated to achieve the desired effect. In refractory cases the use of a cardiac pacemaker should be considered.

### **Heart block (second and third degree)**

Transvenous cardiac pacing.

### **Hypotension**

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

### **Torsade de pointes**

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

### **Dialysis**

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

### **Bronchospasm**

A beta-2-agonist and/or aminophylline.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

### **Mechanism of action**

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

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

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

### **Clinical Trials**

The Electrophysiologic Study Versus Electrographic Monitoring [ESVEM] Trial was designed to compare the choice of antiarrhythmic therapy (**sotalol**, procainamide, quinidine, mexiletine, propafenone, imipramine and pirmenol) by programmed electrical stimulation (PES) suppression versus Holter monitor selection in patients with a history of sustained ventricular tachycardia (VT)/ventricular fibrillation (VF) whose VT/VF were also inducible by PES and PVC's of  $\geq 10$  beats/hour documented by Holter monitoring. Overall acute response, limited to first randomised

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drug, was 39% for **sotalol** and 30% for the pooled other drugs. Acute response rate for first drug randomised using suppression of PES induction was 36% for **sotalol** versus a mean of 13% for the pooled other drugs. Using the Holter monitoring endpoint, **sotalol** yielded 41% response versus 45% for the other drugs combined. Among responders placed on long-term therapy identified acutely as effective, **sotalol**, when compared to the pool of other drugs, had the lowest two-year mortality (13% versus 22%), the lowest two-year VT recurrence rate (30% versus 60%) and the lowest withdrawal rate (38% versus 75-80%). The most commonly used doses of **sotalol** were 320-480 mg/day (66% of patients), with 16% receiving  $\leq$  240 mg/day and 18% receiving  $\geq$  640 mg/day.

### 5.2 Pharmacokinetic properties

#### **Absorption**

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

#### **Distribution**

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

#### **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.

#### **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 h as unchanged **sotalol**. Less than 10% is excreted in the faeces. The mean elimination half-life of **sotalol** is 12.7 + 1.6 (SE) h.

#### **Bioavailability**

The absolute bioavailability on oral administration is close to 100%. The bioavailability is decreased when Sotacor 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 <10mL/min) is a contraindication.

### 5.3 Preclinical safety data

No data available.

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## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

SOTACOR 80mg and 160mg tablets contain the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, maize starch, indigo carmine CI 73015 aluminium lake, colloidal anhydrous silica, stearic acid and magnesium stearate.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store tablets below 30 °C, protect from light and moisture.

### 6.5 Nature and contents of container

Tablets of 80mg & 160 mg in blister packs (PVC/PVDC/Al) of 60 tablets.

### 6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7 MEDICINE SCHEDULE

Prescription Medicine

## 8 SPONSOR

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Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics

58 Richard Pearse Drive

Airport Oaks

Mangere

AUCKLAND

9 DATE OF FIRST APPROVAL

7 October 1976

10 DATE OF REVISION OF THE TEXT

13 May 2019

SUMMARY TABLE OF CHANGES

- Reformat
- Deletion of dosage form solution for injection