# PRODUCT MONOGRAPH

# [Pr]*CO* SOTALOL

Sotalol Hydrochloride

80 mg and 160 mg
BP

Anti-arrhythmic

Cobalt Pharmaceuticals Inc.
6500 Kitimat Road
Mississauga, Ontario
L5N 2B8

Date of Preparation:
August 19, 2005
Date of Revision:
June 20, 2006

Submission Control No: 106618

## Table of Contents

# [Pr]*CO* SOTALOL

## Sotalol hydrochloride

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablet /<br>80 mg, 160 mg, 240 mg | Lactose<br>*For a complete listing see Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

*CO* SOTALOL (sotalol hydrochloride) is indicated for:

- treatment of documented life-threatening ventricular arrhythmias such as sustained ventricular tachycardia.
- treatment of patients with documented symptomatic ventricular arrhythmias when the symptoms are of sufficient severity to require treatment. Because of the proarrhythmic effects of sotalol hydrochloride, its use should be reserved for patients in whom, in the opinion of the physician, the benefit of treatment clearly outweighs the risks.

No anti-arrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most anti-arrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of anti-arrhythmic therapy for all patients with ventricular arrhythmias.

For patients with sustained ventricular tachycardia, *CO* SOTALOL (sotalol hydrochloride) therapy should be initiated in the hospital. Hospitalization may also be required for certain other patients depending on their cardiac status and underlying cardiac disease.

In view of the proarrhythmic effects of sotalol hydrochloride, the use of *CO* SOTALOL in patients with hypertension or angina pectoris is not recommended unless they also require sotalol hydrochloride for the treatment of ventricular arrhythmias.

## CONTRAINDICATIONS

- Patients who are hypersensitive to *CO* SOTALOL (sotalol hydrochloride) or to any ingredient in the formulation or component of the container. For a complete listing of tablet components, see the Dosage Forms, Composition and Packaging section of the product monograph.

- *CO* SOTALOL (sotalol hydrochloride) is contraindicated in patients with bronchial asthma, allergic rhinitis, severe sinus node dysfunction, sinus bradycardia, second and third degree AV block (unless a functioning pacemaker is present), congenital or acquired long QT syndrome, cardiogenic shock, severe or uncontrolled congestive heart failure, hypokalemia, anesthesia with agents that produce myocardial depression and previous evidence of hypersensitivity to sotalol hydrochloride.

## WARNINGS AND PRECAUTIONS

### General

**Mortality**: The results of the Cardiac Arrhythmia Suppression Trial (CAST) in 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. 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 anti-arrhythmic agent.

**Proarrhythmia**: *CO* SOTALOL (sotalol hydrochloride) may cause new or worsen existing arrhythmias. Such proarrhythmic effects range from an increase in frequency of premature ventricular contractions to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes. It is therefore essential that each patient administered *CO* SOTALOL be evaluated clinically and electrocardiographically prior to, and during therapy to determine whether the response to *CO* SOTALOL supports continued treatment. *CO* SOTALOL, like some anti-arrhythmic agents, has been associated with a specific form of arrhythmia, torsade de pointes, which is defined as a polymorphic ventricular tachycardia with prolongation of the QT interval and QRS complexes of changing amplitude that appear to twist around the isoelectric axis. Torsades have been observed more frequently in patients with an elevated baseline QT (>430 msec), on-therapy QT of >500 msec, bradycardia (heart rate < 50 bpm), hypokalemia and hypomagnesemia (see WARNINGS AND PRECAUTIONS - Electrolyte Disturbances) and congestive heart failure. Because of the variable temporal recurrence of arrhythmias, it is not always possible to distinguish between a new or aggravated arrhythmic event and lack of efficacy. Thus, the incidence of drug-related events cannot be precisely determined and the rates of occurrence provided below must be considered approximations. It should be noted that drug-induced arrhythmias may often not be identified until late after starting the drug because of infrequent monitoring. Due to the possibility of proarrhythmic effects, *CO* SOTALOL is not recommended for the treatment of patients with asymptomatic premature

contractions (SEE INDICATIONS AND CLINICAL USE).

Overall in clinical trials with sotalol hydrochloride, 4.3% of 3257 patients experienced a new or worsened ventricular arrhythmia. Of this 4.3%, new or worsened sustained ventricular tachycardia was reported in approximately 1% of patients, and torsade de pointes in 2.4%. Additionally, in approximately 1 % of patients, deaths were considered to be possibly drug-related; such cases, although difficult to evaluate, may have been associated with proarrhythmic events. In patients with a history of sustained ventricular tachycardia, the incidence of torsade de pointes was 4%, and worsened VT was approximately 1%; in patients with other, less serious ventricular arrhythmias and supraventricular arrhythmias, the incidence of experienced torsade de pointes was 1% and 1.4%, respectively.

As shown in the following table, torsade de pointes arrhythmias and the prolongation of QT (QTc) interval were dose-related.

Percent Incidence of Torsade de Pointes and Mean QTc Interval by Dose for Patients with Sustained VT/VF

| Daily Dose (mg) | Incidence of Torsade de pointes | Mean $QT_c$* (msec) |
|---|---|---|
| 80 | 0(69) | 463(17) |
| 160 | 0.5(832) | 467(181) |
| 320 | 1.6(835) | 473(344) |
| 480 | 4.4(459) | 483(234) |
| 640 | 3.7(324) | 490(185) |
| >640 | 5.8(103) | 512(62) |

() Number of patients evaluated
* Highest on-therapy value

In addition to dose and presence of sustained VT, other risk factors for torsade de pointes were gender (females had a higher incidence), excessive prolongation of the QTc interval (see table below) and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure appear to have the highest risk for serious proarrhythmia (7%). Approximately two-thirds of the patients who experienced torsade de pointes spontaneously reverted to their baseline rhythm. The other patients were either converted electrically (D/C cardioversion or overdrive pacing) or were treated with other drugs (see OVERDOSAGE). It is impossible to determine whether some sudden deaths represented episodes of torsade de pointes, but in some instances sudden death followed a documented episode of torsade de pointes. Sotalol hydrochloride therapy was discontinued in most patients who experienced torsade de pointes, but 17% were continued on a lower dose of sotalol. It is recommended that *CO* SOTALOL (sotalol hydrochloride) should be used with particular caution in patients showing a QTc greater than 500 msec on-therapy. A reduction of dose or discontinuation of therapy should be seriously considered when the QTc exceeds 550 msec. Since torsade de pointes is associated with multiple risk-factors, caution should be exercised

regardless of the QTc interval. The table below shows the relationship between the incidence of torsade de pointes to on-therapy QTc and change in QTc from baseline. However, it should be noted that the highest on-therapy QTc was in many cases the one obtained at the time of the torsade de pointes event, therefore, the table overstates the predictive value of a high QTc.

Relationship between QTc Interval Prolongation and Torsade de Pointes

| On-Therapy $QT_c$ Interval (msec) | Incidence of Torsade de pointes |
|---|---|
| <500 | 1.3%(1787) |
| 500-525 | 3.4%(236) |
| 525-550 | 5.6%(125) |
| >550 | 10.8%(157) |

| Change in $QT_c$ Interval from Baseline (msec) | Incidence of Torsade de pointes |
|---|---|
| <65 | 1.6%(1516) |
| 65-80 | 3.2%(158) |
| 80-100 | 4.1%(146) |
| 100-130 | 5.2%(115) |
| >130 | 7.1%(99) |

( ) Number of patients assessed

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; 75% of serious proarrhythmias (torsade de pointes and worsened VT) occurred within 7 days of initiating sotalol hydrochloride therapy, while 60% of such events occurred within 3 days of initiation or a dosage change. Initiating therapy at 80 mg b.i.d. 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 hydrochloride in patients with diminished renal function, by appropriate dose reduction, should also reduce the risk of proarrhythmia (see DOSAGE AND ADMINISTRATION).

**Abrupt Cessation of Therapy:**
Patients should be warned against abrupt interruption or discontinuation of *CO* SOTALOL (sotalol hydrochloride). Hypersensitivity to catecholamines has been observed in patients withdrawn from beta blocker therapy. There have been occasional reports of severe exacerbation of angina pectoris, ventricular arrhythmias and in some cases myocardial infarction following abrupt discontinuation of beta blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, it is prudent when discontinuing chronically administered *CO* SOTALOL, particularly in patients with ischemic heart disease, to carefully monitor the patient and to discontinue *CO* SOTALOL in a stepwise manner or consider the temporary use of an alternate beta-blocker if appropriate. If possible, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully observed. The same frequency of administration should be maintained. If angina markedly worsens or acute coronary insufficiency develops, appropriate therapy should be instituted promptly. Because coronary artery disease is common and may be unrecognized in patients receiving *CO* SOTALOL, abrupt discontinuation in patients with arrhythmias may unmask latent

coronary insufficiency.

**Anaphylaxis:**
While taking beta blockers, patients with a history of anaphylactic reactions to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic or therapeutic.

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and problems with fluid changes. 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 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 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.

**Cardiovascular**
**Congestive Heart Failure**: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure (CHF), and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Moreover, patients with CHF have a higher risk of torsade de pointes (see WARNINGS AND PRECAUTIONS - Proarrhythmia).

In patients with controlled CHF, *CO* SOTALOL (sotalol hydrochloride) should be administered cautiously. The positive inotropic action of digitalis may be reduced when the two drugs are used concomitantly. Both digitalis and sotalol hydrochloride slow AV conduction. If cardiac failure continues despite adequate digitalization, *CO* 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 *CO* SOTALOL.

In clinical trials, new or worsened congestive heart failure (CHF) occurred in 3.3% (n=3257) of patients and led to discontinuation in approximately 1% of patients receiving sotalol hydrochloride. The incidence rate was higher in patients presenting with sustained ventricular tachycardia/fibrillation (4.6%, n=1363), or a prior history of heart failure (7.3%, n=696). Based on a life-table analysis, the one-year incidence of new or worsened CHF was 3% in patients without a prior history and 10% in patients with a prior history of CHF. NYHA Classification was also closely associated to the incidence of new or worsened heart failure in patients receiving sotalol hydrochloride (1.8% in 1395 Class I patients,4.9% in 1254 Class II patients and 6.1% in 278 Class III or IV patients).

**Conduction Disturbances:** Excessive prolongation of the QT interval (>550 msec) can promote serious arrhythmias and should be avoided (see WARNINGS AND PRECAUTIONS - Proarrhythmia). Sinus bradycardia (heart rate less than 50 bpm) occurred in 13% of patients receiving sotalol hydrochloride in clinical trials, and led to discontinuation in about 3% 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:** Caution should be exercised when *CO* SOTALOL (sotalol hydrochloride) is given to patients with recent myocardial infarction. Experience in the use of sotalol hydrochloride in the early stage of recovery from acute myocardial infarction is limited and, at least at high initial doses, not reassuring. In the first 2 weeks following acute myocardial infarction, particular caution is advised. Careful dose titration is especially important, particularly in patients with impaired ventricular function.

In a double-blind, placebo-controlled secondary prevention trial in 1456 post-infarction patients who did not necessarily have ventricular arrhythmias, sotalol hydrochloride was given as a non-titrated dose of 320 mg once daily. The results did not suggest an adverse effect on survival; however, there was a suggestion of excess mortality (3% on sotalol hydrochloride versus 2% on placebo) during the first ten days of the trial. In another trial, where high doses of sotalol hydrochloride (320 mg twice daily) were given to a small number of high-risk post-infarction patients (n=17 randomized to sotalol hydrochloride), there were four fatalities and three serious hemodynamic/electrical adverse events within two weeks of initiating sotalol hydrochloride.

**Sick Sinus Syndrome:** *CO* 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.

**Endocrine and Metabolism**

**Thyrotoxicosis:** In patients with thyrotoxicosis, *CO* SOTALOL may mask the clinical signs of hyperthyroidism or its complications and give a false impression of improvement. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of *CO* SOTALOL which might be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

**Electrolyte Disturbances:** *CO* SOTALOL should not be used in patients with hypokalemia or hypomagnesemia prior to correction of such imbalance, as these conditions can exaggerate the degree of QT prolongation and increase the potential for torsade de pointes. The serum electrolytes must be monitored regularly and more frequently if diuretics are used concomitantly. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or patients receiving concomitant diuretics.

**Diabetes:** *CO* SOTALOL should be administered with caution to patients with history of spontaneous hypoglycemia or to patients with diabetes (especially labile diabetes) receiving insulin or oral hypoglycemic medications. Beta-adrenergic blockers may mask the premonitory

signs and symptoms of acute hypoglycemia; e.g. tachycardia.

**Peri-Operative Considerations**

**Anaesthesia:** It is not advisable to withdraw beta-adrenoceptor blocking agents prior to surgery in the majority of patients. However, care should be taken when using *CO* SOTALOL with anaesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.). Some patients receiving beta-adrenoceptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting the heart and maintaining the heart beat has also been reported. In emergency surgery, since sotalol hydrochloride is a competitive antagonist at beta-adrenoceptor sites, its effects may be reversed, if required, by sufficient doses of such agonists as isoproterenol or noradrenaline.

**Renal**

**Renal Impairment:** Renal function tests should be carried out at appropriate intervals. Caution should be exercised in patients with impaired renal function since *CO* SOTALOL (sotalol hydrochloride) is eliminated mainly via the kidneys through glomerular filtration and to a small degree by tubular secretion. There is a direct relationship between renal function, as measured by serum creatinine or creatinine clearance, and the elimination rate of sotalol hydrochloride. Guidance for dosing in conditions of renal impairment can be found under DOSAGE AND ADMINISTRATION.

**Respiratory**

**Non-Allergic Bronchospasm** (e.g., chronic bronchitis and emphysema): **Patients with bronchospatic diseases should in general not receive beta-blockers.** It is prudent, if *CO* 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 minimized.

**Skin**

**Skin Rashes and Oculomucocutaneous Syndrome:** Various skin rashes and conjunctival xerosis have been reported with beta blockers, including sotalol hydrochloride. A severe syndrome (oculomucocutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one beta-adrenergic-blocking agent (practolol). This syndrome has not been observed with sotalol hydrochloride. Physicians, however, should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

**Special Populations**

**Pregnant Women:** There are no studies in pregnant women. Sotalol hydrochloride has been shown to cross the placenta, and is found in amniotic fluid. There has been a report of subnormal birth weight with sotalol hydrochloride. Therefore, *CO* SOTALOL should be used in pregnancy only if the potential benefit outweighs the potential risks.

**Nursing Mothers:** Sotalol hydrochloride has been found in human milk. Because of potential

adverse reactions from *CO* SOTALOL in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatrics :** The safety and effectiveness of *CO* SOTALOL in children have not been established.

## ADVERSE REACTIONS

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

During clinical trials, 3186 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 important adverse effects are torsade de pointes and other serious new ventricular arrhythmias (see WARNINGS AND PRECAUTIONS), occurring at rates of almost 4% and 1%, respectively, in the VT/VF population. Overall, discontinuation because of unacceptable side-effects was necessary in 17% of all patients in clinical trials, and in 13% of patients treated for at least two weeks. The most common adverse reactions leading to discontinuation of sotalol hydrochloride are as follows: fatigue 4%, bradycardia (<50 bpm) 3%, dyspnea 3%, proarrhythmia 3%, asthenia 2%, and dizziness 2%. Occasional reports of elevated serum liver enzymes have occurred with sotalol hydrochloride therapy but no cause and effect relationship has been established. One case of peripheral neuropathy which resolved on discontinuation of sotalol hydrochloride and recurred when the patient was rechallenged with the drug was reported in an early dose tolerance study. Elevated blood glucose levels and increased insulin requirements can occur in diabetic patients.

Table 1 lists as a function of dosage the most common (incidence of 2% or greater) adverse events, regardless of relationship to therapy and the percent of patients discontinued due to the event, as collected from clinical trials involving 1292 patients with sustained VT/VF.

TABLE 1 Incidence (%) of Adverse Events and Discontinuations

| | DAILY DOSE | | | | | | |
|---|---|---|---|---|---|---|---|
| **Body System** | **160mg (n=832)** | **240mg (n=263)** | **320mg (n=835)** | **480mg (n=459)** | **640mg (n=324)** | **Any Dose* (n=1292)** | **%Pat.Discont. (n=1292)** |
| **Body as a whole** | | | | | | | |
| Infection | 1 | 2 | 2 | 2 | 3 | 4 | <1 |

Incidence (%) of Adverse Events and Discontinuations
DAILY DOSE

| Body System | 160mg (n=832) | 240mg (n=263) | 320mg (n=835) | 480mg (n=459) | 640mg (n=324) | Any Dose* (n=1292) | %Pat.Discont. (n=1292) |
|---|---|---|---|---|---|---|---|
| Fever | 1 | 2 | 3 | 2 | 2 | 4 | <1 |
| Localized pain | 1 | 1 | 2 | 2 | 2 | 3 | <1 |
| **Cardiovascular** | | | | | | | |
| Dyspnea | 5 | 8 | 11 | 15 | 15 | 21 | 2 |
| Bradycardia | 8 | 8 | 9 | 7 | 5 | 16 | 2 |
| Chest pain | 4 | 3 | 10 | 10 | 14 | 16 | <1 |
| Palpitation | 3 | 3 | 8 | 9 | 12 | 14 | <1 |
| Edema | 2 | 2 | 5 | 3 | 5 | 8 | 1 |
| ECG abnormal | 4 | 2 | 4 | 2 | 2 | 7 | 1 |
| Hypotension | 3 | 4 | 3 | 2 | 3 | 6 | 2 |
| Proarrhythmia | <1 | <1 | 2 | 4 | 5 | 5 | 3 |
| Syncope | 1 | 1 | 3 | 2 | 5 | 5 | 1 |
| Heart failure | 2 | 3 | 2 | 2 | 2 | 5 | 1 |
| Presyncope | 1 | 2 | 2 | 4 | 3 | 4 | <1 |
| Peripheral vascular disorder | 1 | 2 | 1 | 1 | 2 | 3 | <1 |
| Cardiovascular disorder | 1 | <1 | 2 | 2 | 2 | 3 | <1 |
| Vasodilation | 1 | <1 | 1 | 2 | 1 | 3 | <1 |
| AICD discharge | <1 | 2 | 2 | 2 | 2 | 3 | <1 |
| Hypertension | <1 | 1 | 1 | 1 | 2 | 2 | <1 |
| **Nervous** | | | | | | | |
| Fatigue | 5 | 8 | 12 | 12 | 13 | 20 | 2 |
| Dizziness | 7 | 6 | 11 | 11 | 14 | 20 | 1 |
| Asthenia | 4 | 5 | 7 | 8 | 10 | 13 | 1 |
| Light-headed | 4 | 3 | 6 | 6 | 9 | 12 | 1 |
| Headache | 3 | 2 | 4 | 4 | 4 | 8 | <1 |
| Sleep problem | 1 | 1 | 5 | 5 | 6 | 8 | <1 |
| Perspiration | 1 | 2 | 3 | 4 | 5 | 6 | <1 |
| Altered consciousness | 2 | 3 | 1 | 2 | 3 | 4 | <1 |
| Depression | 1 | 2 | 2 | 2 | 3 | 4 | <1 |
| Paresthesia | 1 | 1 | 2 | 3 | 2 | 4 | <1 |
| Anxiety | 2 | 2 | 2 | 3 | 2 | 4 | <1 |
| Mood change | <1 | <1 | 1 | 3 | 2 | 3 | <1 |
| Appetite disorder | 1 | 2 | 2 | 1 | 3 | 3 | <1 |
| Stroke | <1 | <1 | 1 | 1 | <1 | 1 | <1 |
| **Digestive** | | | | | | | |
| Nausea/Vomiting | 5 | 4 | 4 | 6 | 6 | 10 | 1 |
| Diarrhea | 2 | 3 | 3 | 3 | 5 | 7 | <1 |

Incidence (%) of Adverse Events and Discontinuation
DAILY DOSE

| Body System | 160mg (n=832) | 240mg (n=263) | 320mg (n=835) | 480mg (n=459) | 640mg (n=324) | Any Dose (n=1292) | *Pat.Discont. (n=1292) |
|---|---|---|---|---|---|---|---|
| Dyspepsia | 2 | 3 | 3 | 3 | 3 | 6 | <1 |
| Abdominal pain | <1 | <1 | 2 | 2 | 2 | 3 | <1 |
| Colon problem | 2 | 1 | 1 | <1 | 2 | 3 | <1 |
| Flatulence | 1 | <1 | 1 | 1 | 2 | 2 | <1 |
| **Respiratory** | | | | | | | |
| Pulmonary problem | 3 | 3 | 5 | 3 | 4 | 8 | <1 |
| Upper respiratory tract problem | 1 | 1 | 3 | 4 | 3 | 5 | <1 |
| Asthma | 1 | <1 | 1 | 1 | 1 | 2 | <1 |
| **Urogenital** | | | | | | | |
| Genitourinary disorder | 1 | 0 | 1 | 1 | 2 | 3 | <1 |
| Sexual dysfunction | <1 | 1 | 1 | 1 | 3 | 2 | <1 |
| **Metabolic** | | | | | | | |
| Abnormal laboratory value | 1 | 2 | 3 | 2 | 1 | 4 | <1 |
| Weight change | 1 | 1 | 1 | <1 | 2 | 2 | <1 |
| **Musculoskeletal** | | | | | | | |
| Extremity pain | 2 | 2 | 4 | 5 | 3 | 7 | <1 |
| Back pain | 1 | <1 | 2 | 2 | 2 | 3 | <1 |
| **Skin & Appendages** | | | | | | | |
| Rash | 2 | 3 | 2 | 3 | 4 | 5 | <1 |
| **Hematologic** | | | | | | | |
| Bleeding | 1 | <1 | 1 | <1 | 2 | 2 | <1 |
| **Special Senses** | | | | | | | |
| Visual problem | 1 | 1 | 2 | 4 | 5 | 5 | <1 |

*Because patients are counted at each dose level tested, the "Any Dose" column cannot be determined by adding across the doses.

**Post-Market Adverse Drug Reactions**

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, incoordination, vertigo, paralysis, thrombocytopenia, eosinophilia, leukopenia, photosensitivity

reaction, fever, pulmonary edema, hyperlipidemia, 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 characterized 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 nonthrombocyto-penia purpura.

**Gastrointestinal:** Mesenteric arterial thrombosis; ischemic colitis.

**Other:** Peyronie's disease, Raynaud's phenomenon.

## DRUG INTERACTIONS

### Overview

**Anti-arrhythmics:** Class Ia anti-arrhythmic drugs, such as disopyramide, quinidine and procainamide, and Class III drugs (e.g., amiodarone) are not recommended as concomitant therapy with *CO* SOTALOL (sotalol hydrochloride) because of their potential to prolong refractoriness (see WARNINGS AND PRECAUTIONS). There is only limited experience with the concomitant use of Class IB or Ic anti-arrhythmics. Additive Class II effects would also be anticipated with the use of other beta-blocking agents concomitantly with *CO* SOTALOL.

**Drugs prolonging the QT Interval:** *CO* SOTALOL should also be given with extreme caution in conjunction with other drugs known to prolong the QT interval, such as Class I and Class III anti-arrhythmics, phenothiazines, tricyclic antidepressants, terfenadine, astemizole, erythromycin, lithium and liquid protein diets.

### Drug-Drug Interactions

**Digoxin:** Single and multiple doses of *CO* SOTALOL (sotalol hydrochloride) do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol hydrochloride treated patients also receiving digoxin. It is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in the patients receiving digoxin.

**Calcium blocking drugs:** *CO* SOTALOL should be administered with caution in conjunction with calcium blocking drugs because of possible synergistic impairment of atrioventricular conduction and of ventricular function. Additionally, concomitant use of these drugs may have additive effects on blood pressure, possibly leading to hypotension.

**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 treated with *CO* SOTALOL plus a catecholamine depletor should therefore be closely monitored for evidence of hypotension and/or marked bradycardia, which may produce syncope.

**Insulin and oral hypoglycemics:** Hypoglycemia and hyperglycemia may occur and the dosage of antidiabetic drug should be adjusted accordingly (See WARNINGS AND PRECAUTIONS - Diabetes).

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

**Beta-2-receptor stimulants:** Beta-agonists such as salbutamol, terbutaline and isoprenaline may have to be administered in increased dosages when used concomitantly with *CO* SOTALOL.

**Drug-Food Interactions**

When sotalol hydrochloride is given with a standard meal, the absorption of sotalol hydrochloride is reduced by approximately 20% compared to that in the fasting state.

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

- Renal Impairment: Because sotalol hydrochloride is excreted predominantly in urine and its elimination half-life is prolonged in conditions of renal impairment, a longer duration of dosing is required to reach steady state. The dosing interval of *CO* SOTALOL should then be modified, when creatinine clearance is <60 mL/min, as shown in the following table.

| Creatinine Clearance (mL/min) | Dosing Interval (hours) |
|---|---|
| > 60 | 12 |
| 30-60 | 24 |
| 10-30 | 36-48 |
| < 10 | Dose should be individualized |

  Dose increases in renal impairment should only be done after administration of at least 5 or 6 doses at appropriate intervals.

- Transfer to and from *CO* SOTALOL: Based on theoretical considerations rather than experimental data, the following suggestion is made: when transferring patients from another anti-arrhythmic drug to *CO* SOTALOL or from *CO* SOTALOL to another anti-arrhythmic agent, allow at least 3 to 4 half-lives to elapse for the drug being discontinued before starting the alternative drug at the usual dosage. In patients where withdrawal of a previous anti-

arrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

**Recommended Dose and Dosage Adjustment**

Dosage of *CO* SOTALOL should be adjusted gradually, allowing 2-3 days between dosing increments in order to attain steady-state plasma concentrations 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 dose is 80 mg twice daily. If needed, this dose may be increased, 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 arrhythmias may require doses as high as 480-640 mg/day; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, in particular proarrhythmias. Because of the long elimination half-life of *CO* SOTALOL, dosing on more than a twice daily regimen is not usually necessary.

Patients experiencing bradycardia or hypotension on initial administration of *CO* SOTALOL should be removed from therapy; *CO* SOTALOL may be later reintroduced at a lower dose. A dose reduction may also be advisable to alleviate symptoms of weakness and dizziness in cases where blood pressure remains low after more than a month of therapy.

**Administration**

*CO* SOTALOL (sotalol hydrochloride), when used for the treatment of documented life-threatening ventricular arrhythmias, should be initiated and dose increased in a hospital with facilities for cardiac rhythm monitoring and assessment (see INDICATIONS AND CLINICAL USE). *CO* SOTALOL should be administered only after appropriate clinical assessment, and the dosage of *CO* SOTALOL must be individualized on the basis of therapeutic response and tolerance. The usefulness of monitoring plasma level for optimization of therapy has not been established. Proarrhythmic events can occur not only at the initiation of therapy, but also with each upward dosage adjustment.

## OVERDOSAGE

Intentional or accidental overdosage with sotalol hydrochloride has rarely resulted in death. The most common signs to be expected are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia. In cases of massive intentional overdosage (2-16 grams) with sotalol hydrochloride the following clinical findings were seen: hypotension, bradycardia, prolongation of QT interval, torsade de pointes, ventricular tachycardia, and premature ventricular complexes. If overdosage occurs, therapy with *CO* SOTALOL (sotalol hydrochloride) should be discontinued. Close monitoring of the electrocardiogram in patients with suspected sotalol hydrochloride intoxication is essential. Because of the lack of protein binding, hemodialysis is useful for reducing sotalol hydrochloride plasma concentrations. Patients should be carefully observed until QTc intervals are normalized. Every effort should be made to correct promptly metabolic and electrolyte imbalances which might contribute to the initiation of ventricular arrhythmias (see WARNINGS AND PRECAUTIONS).

If required, the following therapeutic measures are suggested:

1. Bradycardia: atropine, another anticholinergic drug, a beta-adrenergic agonist or transvenous cardia pacing.
2. Heart Block (second and third degree): Isoproterenol or transvenous cardiac pacemaker.
3. Congestive Heart Failure: Conventional therapy.
4. Hypotension: (depending on associated factors) Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis (see PRECAUTIONS).
5. Bronchospasm: Aerosolized beta-2-receptor stimulant or aminophylline.
6. Hypoglycemia: Intravenous glucose.
7. Torsade de pointes: Epinephrine, magnesium sulfate, transvenous cardiac pacing, DC cardioversion.

It should be remembered that *CO* SOTALOL (sotalol hydrochloride) is a competitive antagonist of isoproterenol and, hence, large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of *CO* SOTALOL. However, the complication of excess isoproterenol should not be overlooked.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Sotalol hydrochloride has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) anti-arrhythmic properties. *CO* SOTALOL is a racemic mixture of d- and l-sotalol. Both isomers have similar Class III anti-arrhythmic effects, while the l-isomer is responsible for virtually all of the beta-blocking activity. Sotalol hydrochloride is non-cardioselective and is not associated with partial agonist or membrane stabilizing activity. Whereas significant beta-blockade may occur at oral doses as low as 25 mg, Class III effects are seen at daily doses of 160 mg and above. The anti-arrhythmic activity of sotalol hydrochloride appears to be primarily due to the drug's Class III property, based on animal models.

Pharmacologically, in addition to its anti-arrhythmic properties, sotalol hydrochloride has also antihypertensive and anti-anginal properties.

### Pharmacodynamics

**Electrophysiology:** Sotalol hydrochloride prolongs the plateau phase of the cardiac action potential in the isolated myocyte, as well as in isolated tissue preparations of ventricular and atrial muscle (Class III activity). In intact animals it slows heart rate, decreases A-V nodal conduction and increases the refractory periods of atrial and ventricular muscle and conduction tissue.

In man, the Class II (beta-blockade) electrophysiological effects of sotalol hydrochloride are manifested by increased sinus cycle length, decreased AV nodal conduction and increased AV nodal refractoriness. The Class III electrophysiological effects in man include prolongation of

the atrial and ventricular monophasic action potentials, and effective refractory period prolongation of atrial muscle, ventricular muscle, and atrioventricular accessory pathways (where present) in both the anterograde and retrograde directions. With oral doses of 160 to 640 mg/day, the surface ECG shows dose-related mean increases of 40-100 msec in QT and 10-40 msec in QTc. No significant alteration in QRS interval is observed.

In a small study (n=25) of patients with implanted defibrillators treated concurrently with sotalol hydrochloride, the average defibrillatory threshold was 6 joules (range 2-15 joules) compared to a mean of 16 joules for a non-randomized comparative group primarily receiving amiodarone.

In a randomized clinical trial [Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Trial] comparing choice of anti-arrhythmic therapy by PES suppression versus Holter monitor selection (in each case followed by treadmill exercise testing) in patients with a history of sustained VT/VF who were also inducible by PES, the effectiveness acutely and chronically of sotalol hydrochloride was compared with 6 other drugs (procainamide, quinidine, mexiletine, propafenone, imipramine and pirmenol). Overall response, limited to first randomized drug, was 39% for sotalol hydrochloride and 30 % for the pooled other drugs. Acute response rate for first drug randomized using suppression of PES induction was 36% for sotalol hydrochloride versus a mean of 13% for the other drugs. Using the Holter monitoring endpoint (complete suppression of sustained VT, 90% suppression of NSVT, 80% suppression of VPC pairs, and at least 70% suppression of VPCs), sotalol hydrochloride yielded 41% response versus 45% for the other drugs combined. Among responders placed on long-term therapy identified acutely as effective (by either PES or Holter), sotalol hydrochloride, 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 about 75-80%). The most commonly used doses of sotalol hydrochloride in this trial were 320-480 mg/day (66% of patients), with 16% receiving 240 mg/day or less and 18% receiving 640 mg or more.

It cannot be determined, however, in the absence of a controlled comparison of sotalol hydrochloride versus no pharmacologic treatment (e.g., in patients with implanted defibrillators) whether sotalol hydrochloride response causes improved survival or identifies a population with a good prognosis.

**Hemodynamics:** In a study of systemic hemodynamic function measured invasively in 12 patients with a mean left ventricular (LV) ejection fraction of 37% and ventricular tachycardia (9 sustained and 3 non-sustained), a median dose of 160 mg twice daily of sotalol hydrochloride produced a 28% reduction in heart rate and a 24% decrease in cardiac index at 2 hours post dosing at steady-state. Concurrently, systemic vascular resistance and stroke volume showed non-significant increases of 25% and 8%, respectively. Pulmonary capillary wedge pressure increased significantly from 6.4 mmHg to 11.8 mmHg in the 11 patients who completed the study. One patient was discontinued because of worsening congestive heart failure. Mean arterial pressure, mean pulmonary artery pressure and stroke work index did not significantly change. Exercise and isoproterenol induced tachycardia are antagonized by sotalol hydrochloride and total peripheral resistance increases by a small amount.

In hypertensive patients, sotalol hydrochloride produces significant reductions in both systolic and diastolic blood pressures. Although sotalol hydrochloride is usually well-tolerated hemodynamically, caution should be exercised in patients with marginal cardiac compensation as deterioration in cardiac performance may occur. (See WARNINGS AND PRECAUTIONS - Congestive Heart Failure).

## Pharmacokinetics

**Absorption:** In healthy subjects: The oral bioavailability of sotalol hydrochloride is 90-100%. After oral administration, peak plasma concentrations are reached in 2.5 to 4 hours, and steady-state plasma concentrations are reached within 2 to 3 days. Over the dosage range of 160-640 mg/day, sotalol hydrochloride displays dose proportionality with respect to plasma concentrations.

**Distribution:** Distribution occurs to a central (plasma) and to a peripheral compartment, with a mean elimination half-life of 7-15 hours.

**Metabolism:** Sotalol hydrochloride does not bind to plasma protein and is not metabolized. The pharmacokinetics of the d and l enantiomers of sotalol hydrochloride are essentially identical. Sotalol hydrochloride crosses the blood brain barrier poorly. In one study, mean cerebrospinal fluid concentrations following a single oral dose ranged from 5% to 28% of those observed in plasma.

**Excretion:** Sotalol hydrochloride is eliminated principally via the kidneys through glomerular filtration and to a small degree by tubular secretion.

## Special Populations and Conditions

**Geriatrics:** Age alone does not significantly alter the pharmacokinetics of sotalol hydrochloride, but impaired renal function in elderly patients can increase the terminal elimination half-life, resulting in increased drug accumulation.

**Hepatic Insufficiency:** In hepatically impaired patients Sotalol hydrochloride is not subject to first-pass metabolism. Therefore, patients with hepatic impairment show no alteration in clearance of sotalol hydrochloride.

**Renal Insufficiency:** In renally impaired patients excretion is predominantly via the kidney in the unchanged form, and therefore, lower doses are necessary in renal impairment (see DOSAGE and ADMINISTRATION and PRECAUTIONS).

**Effect of food:** When sotalol hydrochloride is given with a standard meal, the absorption of sotalol hydrochloride is reduced by approximately 20% compared to that in the fasting state.

## STORAGE AND STABILITY

*CO* SOTALOL tablets should be stored in tight, light-resistant containers at controlled room temperature (15-30° C).

## DOSAGE FORMS, COMPOSITION AND PACKAGING

*CO* SOTALOL Tablets are available in three strengths, namely 80 mg and 160 mg. Tablets are embossed on one side and scored on the other.

**80 mg tablets:**
Each light blue, capsule-shaped tablet embossed "ICN-S31" contains 80 mg of sotalol hydrochloride, BP. **Non-medicinal Ingredients**: colloidal silicon dioxide NF, FD&C blue #2 Aluminium Lake, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF.

**160 mg tablets:**
Each light blue, capsule-shaped tablet embossed "ICN-S32" contains 160 mg of sotalol hydrochloride, BP. **Non-medicinal Ingredients**: colloidal silicon dioxide NF, FD&C blue #2 Aluminium Lake, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF.

*CO* SOTALOL tablets are available in bottles of 100 and 500 tablets.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

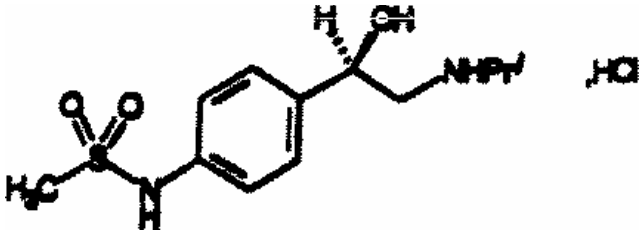
Proper name: sotalol hydrochloride

Chemical name: (1)methanesulfonamide,N-[4-[1-hydroxy-2-[(1-ethylethyl) amino]ethyl]-phenyl]-,monohydro-chloride; (2)4'-[1-Hydroxy-2-(isopropylamino)ethyl]methane sulfonanilide monohydrochloride

Molecular formula: $C_{12}H_{20}N_2O_3S.HCl$

Molecular Weight: 308.83

Structural Formula:



**and enantiomer**

Physicochemical properties: Sotalol hydrochloride is a white, crystalline solid which melts at 209-210° C. It is freely soluble in water (with a pH of approximately 5.3), propylene glycol, and ethanol but is only slightly soluble in chloroform.

## CLINICAL TRIALS

**Comparative Bioavailability Studies:** In a bioavailability study comparing Bristol Laboratories of Canada's Sotacor 160 mg tablets and ICN Canada's Rylosol 160 mg tablets in healthy men, revealed bioequivalent data for both drugs.

**Summary Table of the Comparative Bioavailability Data**
**Rylosol**
**(160 mg)**
**From measured data**
**Geometric Mean**
**Arithmetic Mean (CV %)**

| Parameter | Test<br>Rylosol<br>ICN Canada | Reference<br>Sotacor<br>Bristol Laborat.<br>Canada | % Ratio of Geometric Means |
|---|---|---|---|
| $AUC_T$<br>(ng.hr/mL) | 12294.1<br>12532.8(20) | 12911.7<br>13092.3(18) | 0.95 |
| $AUC_I$<br>(ng.hr/mL) | 12745.3<br>12980.0(19) | 13394.3<br>13567.7(17) | 0.95 |
| $C_{MAX}$<br>(ng/mL) | 1115.7 | 1221.8 | 0.91 |
| $T_{MAX}$[§]<br>(h) | 2.9<br>(40) | 2.7<br>(31) | |
| $T_{½}$[‖]<br>(h) | 11.3<br>(27.7) | 11.5<br>(27.1) | |

§ Expressed as the arithmetic mean (CV%)
‖ Expressed as the arithmetic mean (CV%)

## DETAILED PHARMACOLOGY

In vitro, sotalol hydrochloride antagonized the chronotropic and inotropic effects of isoproterenol on isolated spontaneously beating atria and perfused cat heart, and antagonized the relaxant action of isoproterenol on the spontaneous contractions of the "diestrus" rat uterus, the intrinsic tonus and histamine-induced spasms of the guinea pig. In anesthetized dogs, sotalol hydrochloride administered intravenously had a negative inotropic and chronotropic action. Sotalol hydrochloride completely blocked the changes in heart rate, cardiac output, left ventricular work and total peripheral resistance induced by isoproterenol, and had decreasing

effects on respiration, blood pressure and heart rate similar to propranolol.

Sotalol hydrochloride reduced the mortality rate in dogs with ligation of a coronary artery, which was thought to be due to beta-blockade, suppressed the actinine, coronary-artery-ligation and hydrocarbon-epinephrine-induced arrhythmias and suppressed atrial flutter and restored normal sinus rhythm.

The ECG is not changed with the exception of a minor prolongation of the PR interval. Sotalol hydrochloride will inhibit isoproterenol-induced tachycardia and exercise tachycardia. In patients receiving right and left heart catheterization the drug produced a significant reduction in heart rate and cardiac output, but stroke volume was unchanged. Systemic arterial and pulmonary pressures were not significantly altered, but indices of myocardial function were reduced. Nine patients with angina pectoris, studied at a constant treadmill speed, showed an increase in exercise time after sotalol hydrochloride i.v. 0.5 mg/kg of 80 to 165 seconds.

Sotalol hydrochloride has no local anesthetic action on rabbit eye or guinea pig skin at concentrations ranging from 0.1 to 6.4%. The intravenous injection of sotalol hydrochloride in anesthetized dogs caused reduction in pulmonary blood flow, increase in pulmonary vascular resistance and interference in the increase of pulmonary flow in response to isoproterenol, anoxia and electrical stimulation of thoracic sympathetic nerve.

In 13 patients suffering from obstructive lung disease the administration of sotalol hydrochloride provoked a significant increase of the airway resistance and a decrease of the FEV. Sotalol hydrochloride does not alter intraocular pressure.

## TOXICOLOGY

### Acute Toxicity

| Species | Sex | No. of Animals | Route | LD50 mg/kg | # of Deaths |
|---|---|---|---|---|---|
| Mice | M | 50 | Oral | 2600 | 15 |
| | M | 130 | i.p. | 670<br>645 | 36 |
| | M | 40 | i.v. | 174 | 19 |
| Rats | M | 90 | Oral | 3450 | 13 |
| | M | 30 | i.p. | 680 | - |
| Rabbits | M&F | 12 | Oral | 1000 | 6 |
| | M&F | 12 | i.v. | 78 | 3 |
| Dogs | M&F | 6 | Oral | 50* | - |
| | M&F | 18 | i.p. | 330 | 4 |
| | M&F | 24 | i.v. | 240 | 5 |

*Emesis occurred at doses of 100 and 200 mg/kg; LD50 could not be determined.

Signs of toxicity were: ataxia, labored respiration, loss of righting reflex, depression,

hypoactivity, asphyxial movements, convulsions.

The following signs were also reported in some species: ptosis, increased respiratory depth; Straub's tail reaction, head and body shaking, emesis, bradycardia, cyanosis, relaxed nicitating membrane, moderate tearing, watery stools, weak heart beat, profuse salivation, coarse tremors and piloerection.

**Chronic Toxicity**

| Species | Sex | Route of Administr | Dosage mg/kg/day | Time Period | Toxicity Signs |
|---|---|---|---|---|---|
| Mice | F | oral | 500 | 6 mths | none |
| Rats | M&F | oral | 0; 50; 250; 1250 | 1 year | ataxia, depression, slightly depressed growth & food efficiency, increased spleen weight |
| Rats | M&F | oral | 0; 75; 275; 975 or 1000 | 1 year | decrease in body weight gain (dose related); increases in heart dimensions of male rats, cartilagenous metaplasia in heart sections |
| Dogs | M&F | oral | 0; 5; 15; 45; 60 or 70 | 1 year | decrease in heart rate (dose-related) |

**Reproductive Studies**
The oral administration of sotalol hydrochloride of 500 mg/kg/day on days 3, 5, 7, 8, 10 and 12 of gestation in pregnant mice and of 100 mg/kg on day 6 through 16 in pregnant rabbits had no effect on the incidence of successful pregnancies, litter size, incidence of stillborn, weight of newborn, growth of newborn to weaning post-natal survival.

Male rats fed 20 or 142 mg/kg of sotalol hydrochloride for 70 weeks exhibited no drug related decrease in reproductive performance.

Oral administration of 1000 mg/kg to male and female rats prior to mating had no adverse effect upon the fertility of female rats, the post-natal survival and development of the offspring. Female rats had fewer pups per litter than control rats. No evidence of teratogenicity was noted.

The continuous administration of sotalol hydrochloride to pregnant rats (20, 140, or 1000 mg/kg) and to pregnant rabbits (100, 150, or 225 mg/kg) during the critical period of organogenesis for each species had no teratogenic or embryotoxic effect on their offspring. In rats, 1000 mg/kg/day of sotalol hydrochloride increased the number of early resorption, while at 14 times the

maximum dose, no increase in early resorptions was noted.

**Tumorigenic Tests**
Sotalol hydrochloride, orally administered to mice at doses of 0, 100, 300 or 600 mg/kg/day for a period of 18 months in two different studies, did not show statistical differences in total or specific tumors when compared to control groups.

Sotalol hydrochloride, orally administered to rats at doses of 0, 137, or 275 mg/kg/day for a period of 18 months, did not show statistical differences in the incidence of neoplasms when compared to control groups.

**REFERENCES**


1. Anttila M., Arstila M., Pfeffer M., Tikkanen R., Vallinkoski V.and Sundquist H. Human pharmacokinetics of Sotalol. Acta Pharmacol et Toxicol 1976;39:118-128
2. Bergamaschi M., Shanks R.G., Caravaggi A.M. and Mandelli V. A comparison of the cardiovascular actions of four adrenergic ß-receptor blocking agents in resting, conscious dogs. Amer Heart J 1971; 82 (3):338-351
3. Berglund G., Descamps R. and Thomis J.A. Pharmacokinetics of sotalol after chronic administration to patients with renal insufficiency. Eur J Clin Pharmcol (Germany) 1980;18(4):321-326
4. Blair A.D., Burgess E.D., Maxwell B. and Cutler R.E. Sotalol kinetics in renal insufficiency. Clin Pharmacol Ther (US); 1981; 29(4):457- 463
5. Brown H.C., Carruthers S.G., Kelly J.G., McDevitt D.G. and Shanks R. G. Observations on the efficacy and pharmacokinetics of sotalol after oral administration. Eur J Clin Pharmacol 1976;09(5/6):367-372
6. Gibson D.G. Pharmacodynamic properties of ß-adrenergic receptor blocking drugs in man. Drugs 1974;7:8-38
7. Gooding P.G. and Berman E. An evaluation of sotalol, a ß-blocking agent, in patients with angina pectoris. Postgrad Med J 1974;50(590):734-736
8. Griffith M.J., Linker N.J., Garratt C.J., Ward D.E. and Camm A.J. Relative efficacy and safety of intravenous drugs for termination of sustained ventricular tachycardia. Lancet 1990; 336 (8716):670-673
9. Julian D.G., Prescott R.J., Jackson F.S. and Szekely P. Controlled trial of sotalol for one year after myocardial infarction. Lancet 1982; 1 (8282):1142-1147
10. Kunze K.P., Schluter M., and Kuck K.H. Sotalol in patients with Wolff-Parkinson-White syndrome. Circulation (US) 1987;75(5): 1050-1057
11. Latour Y., Dumont G., Brosseau A., LeLorier J. Effects of sotalol in twenty patients with

cardia arrhythmias. Int J Clin Pharmacol Biopharm 1977;15(6):275-278

12. Lish P.M., Shelanski M.V., LaBudde J.A. and Williams W.R. Inhibition of cardiac chronotropic action of isoproterenol by sotalol (MJ 1999) in rat, dog and man. Curr Ther Res Clin Exp 1967;9(6): 311-324
13. Lish P.M., Weikel J.H. and Dungan K.W. Pharmacological and toxicological properties of two new ß-adrenergic receptor antagonists. J Pharmacol Exp Ther 1965; 149 (2):161-173
14. McDevitt D.G., Brown H.C., Carruthers S.G., and Shanks R.G. Influence of intrinsic sympathomimetic activity and cardioselectivity on beta adrenoceptor blockade. Clin Pharm & Ther 1976;21(3):556- 566
15. Parvinen I. and Paukkala E. Comparison of once and twice daily administration of Sotalol in the treatment of hypertension. Eur J Clin Pharmacol 1979;15(5):293-298
16. Puri P.S. and Bing R.J. Effects on myocardial contractility, hemodynamics and cardiac metabolism of a new beta-adrenergic blocking drug, Sotalol. Dis Chest 1969; 55(3):235-239
17. Rice A.J., Ferguson R.K., Delle M., and Wilson W.R. Comparative beta-blocking activities and effects on sodium excretion of sotalol and propranolol. Clin Pharm & Ther 1970;11(4):567-573
18. Schnelle K., Klein G. and Schinz A. Studies on the pharmacokinetics and pharmacodynamics of the beta-adrenergic blocking agent sotalol in normal man. J Clin Pharmacol 1979;19(8/9 PT2):516-522
19. Stanton H.C., Kirchgessner T. and Parmenter K. Cardiovascular pharmacology of two new ß-adrenergic receptor antagonists. J Pharmacol Exp Ther 1965; 149 2):174-182
20. Sunquist H., Anttila M., and Arstila M. Antihypertensive effects of practolol and sotalol. Clin Pharmacol Ther 1974;16(3):465-472
21. Sundquist H.K., Anttila M., Forsstrom J. and Kasanen A. Serum levels and half-life of sotalol in chronic renal failure. Ann Clin Res 1975;7(6):442-446
22. Tjandramaga T.B., Thomas J., Verbeeck R., Verbesselt R., Verberckmoes R. and De

Schepper P.J. The effect of end-stage renal failure and haemodialysis on the elimination kinetics of sotalol. Br J Clin Pharmacol 1976;3(2):259-265

23. Product Monograph: Sotacor (sotalol hydrochloride) Bristol-Myers Squibb, April 13, 1994

**PART III: CONSUMER INFORMATION**

[Pr]*CO* SOTALOL
Sotalol hydrochloride

This leaflet is part III of a three-part "Product Monograph" published when [Pr]*CO* SOTALOL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about [Pr]*CO* SOTALOL. Contact your doctor or pharmacist if you have any questions about the drug.

## ABOUT THIS MEDICATION

*CO* SOTALOL is a brand name for the drug Sotalol Hydrochloride. It belongs to the group of drugs known as beta-blockers.

What the medication is used for:
*CO* SOTALOL is used to treat irregular and troublesome heartbeats that can be dangerous for you and in some circumstances can even cause death.

What it does:
[Pr]*CO* SOTALOL can help your heart to beat in a more normal way.

When it should not be used:
When you experience the following:
• symptoms of heart failure (such as swelling of the ankles or legs with shortness of breath on exercise);
• shortness of breath in lung disease (such as asthma, chronic bronchitis or emphysema);
• severe slowing of heart beat without an implanted artificial pacemaker;
• serious kidney problems.
• chest pain

What the medicinal ingredient is:
Sotalol hydrochloride.

What the important nonmedicinal ingredients are:
Colloidal silicon dioxide, D&C Yellow #10 Aluminium Lake, FD&C Blue #1 Aluminium Lake, FD&C blue #2 Aluminium Lake, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

What dosage forms it comes in:
Tablets 80 mg and 160 mg.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

[Pr]*CO* SOTALOL is not appropriate for everyone with irregular heartbeats. If you have atrial fibrillation (a specific type of irregular heartbeat), you and your doctor should carefully discuss the benefits and risks of [Pr]*CO* SOTALOL and whether your symptoms are troublesome enough for you to start taking [Pr]*CO* SOTALOL. In some patients treated with [Pr]*CO* SOTALOL for atrial fibrillation, sotalol may cause a different type of abnormal heartbeat that can be dangerous, and in rare instances can even cause death.

Check with your doctor if you want to drink alcohol, while you are taking *CO* SOTALOL. Chronic use of alcohol may lead to low levels of magnesium which is cause of very serious adverse event.

Talk to your doctor or pharmacist before using salt substitutes containing potassium. If your doctor prescribes a low salt or low sodium diet, follow the directions carefully.

BEFORE you use [Pr]*CO* SOTALOL talk to your doctor or pharmacist if:

- You perform hazardous activities such as driving, operating machinery, or any other hazardous activities. Sotalol hydrochloride may cause drowsiness, dizziness, and blood pressure changes. If you experience drowsiness or dizziness, avoid these activities. Remember alcohol can add to the drowsiness caused by *CO* SOTALOL.
- You have heart, lung, kidney and liver diseases or experience symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, or vomiting, or loss of appetite or thirst;
- You have a history of anaphylactic reactions;
- You are pregnant, plan to become pregnant or a nursing mother; if you become pregnant while taking *CO* SOTALOL, contact your doctor or pharmacist.
- you are taking prescription and non-prescription drugs, herbal remedies, complementary medicines, or an operation or a dental surgery is anticipated;
- you had an allergic reaction with one of [Pr]*CO* SOTALOL ingredients.
- You are suffering from asthma or breathing difficulties.
- You are suffering from severe diarrhoea.

## INTERACTIONS WITH THIS MEDICATION

*CO* SOTALOL interacts with other drugs including those used for diabetes and heart diseases.

- Do not take medicinal products (prescription and non-prescription drugs) or natural/herbal remedies without consulting your doctor or pharmacist as they may aggravate your condition. Always carry a list of medicines you are taking, and make sure that any new or different health care provider be informed about this list in order to get a safe medicine not interacting with any other one included in that list.

## PROPER USE OF THIS MEDICATION

*CO* SOTALOL should be taken exactly as directed by your doctor or pharmacist. Try to take the medicine at the same times each day to avoid missing any doses.

Never take more than the prescribed dose. Do not stop taking *CO* SOTALOL without consultation with your doctor or pharmacist. They may want to reduce your dose gradually.

*CO* SOTALOL is prescribed for certain medical conditions. Never give to others even if their conditions appears to be the same as yours.

Usual dose:
The initial dosing of [Pr]*CO* SOTALOL should be done in the hospital as your heartbeat closely watched by health care professionals for the first few days. At home, it is important that you take the exact dose your doctor has prescribed for you at regular time with or without food.

Overdose:
If at any time, you experience symptoms of a sotalol overdose such as slow heartbeat or a different type of abnormal heart beat, wheezing, shortness of breath, fainting, dizziness, weakness, call immediately your doctor or go to the nearest hospital emergency room.

Missed Dose:
Do not miss a dose as it could be dangerous. However, if a dose is missed, you should not double the next dose. Instead, you should wait until the next scheduled dose, and resuming the prescribed regimen at that time.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The common documented side effects are slowing the heart beat, shortness of breath and fatigue. It is important that you keep your doctor informed of all side effects, especially if you experience any for more than few days. However, keep taking [Pr]*CO* SOTALOL until your doctor tells you to stop.

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Common | Dyspnea / shortness of breath | ✓ | | |
| | Bradycardia / slowing of heart beat | ✓ | | |
| | Fatigue / tiredness | ✓ | | |
| | New tachycardia / new fast heart beat | | ✓ | |
| | Light-headedness | | ✓ | |
| | Fainting | | ✓ | |
| Uncommon | Diarrhea | ✓ | | |
| | Vomiting | ✓ | | |
| | Loss of appetite | ✓ | | |
| | Thirst | ✓ | | |

*This is not a complete list of side effects. For any unexpected effects while taking [Pr]CO* SOTALOL*, contact your doctor or pharmacist immediately.*

## HOW TO STORE IT

[Pr]*CO* SOTALOL tablets should be stored at room temperature (15 to 30°C) away from moisture and heat. Tablets should be kept in tightly closed container. Keep *CO* SOTALOL out of reach of children. Do not keep or use *CO* SOTALOL after the expiry date indicated on the container.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

***NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals are available by contacting the sponsor, Cobalt Pharmaceuticals Inc., at: 1-866-254-6111

This leaflet was prepared by Cobalt Pharmaceuticals Inc.

Last revised: June 20, 2006