PRODUCT MONOGRAPH

SANDOZ SOTALOL
(Sotalol Hydrochloride)

80 mg and 160 mg Tables BP

Antiarrhythmic

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Date of Preparation
May 1, 2006

Control # 105545

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80 mg and 160 mg

THERAPEUTIC CLASSIFICATION

Antiarrhythmic

ACTIONS AND CLINICAL PHARMACOLOGY

Sotalol hydrochloride has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol hydrochloride is a racemic mixture of d- and l-sotalol. Both isomers have similar Class III antiarrhythmic effects, while the l-isomer is responsible for virtually all of the beta-blocking activity. Sotalol 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 antiarrhythmic activity of sotalol appears to be primarily due to the drug's Class III property, based on animal models.

Pharmacologically, in addition to its antiarrhythmic properties, sotalol hydrochloride also has antihypertensive and antianginal properties.

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 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 QT_c. 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 antiarrhythmic 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 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 VPC's), 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 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 is usually well tolerated hemodynamically, caution

should be exercised in patients with marginal cardiac compensation as deterioration in cardiac performance may occur (see WARNINGS: Congestive Heart Failure).

Pharmacokinetics

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 attained within 2-3 days. Over the dosage range of 160-640 mg/day, sotalol hydrochloride displays dose proportionality with respect to plasma concentrations. Distribution occurs to a central (plasma) and to a peripheral compartment, with a mean elimination half-life of 7 - 15 hours.

Sotalol hydrochloride does not bind to plasma proteins and is not metabolized. The pharmacokinetics of the d and l enantiomers of sotalol are essentially identical. Sotalol 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.

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).

In Hepatically-Impaired Patients: Since sotalol hydrochloride is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol hydrochloride.

In Elderly Patients: Age per se 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.

Effect of Food: When sotalol hydrochloride was administered with a standard meal, the absorption was reduced by approximately 20% compared to that in the fasting state.

A blinded, randomized, cross-over, single-dose bioavailability study was conducted in 18 healthy male volunteers to compare the bioavailability of Sandoz Sotalol (160 mg) tablets to Sotacor® (160 mg) tablets. The pharmacokinetic results are listed in the table that follows.

Summary Table of the Sotalol HCl 160 mg Tablet
Comparative Bioavailability Data
(Dose: 160 mg) (From measured data)

	Geometric Mean* Arithmetic Mean (CV%)**		
Parameter	**Sandoz Sotalol**	**Sotacor®**	**Ratio of Means**
AUC_T	16237	16523	98.3
(ng•hr/mL)	16729 (22)	16786 (19)	
AUC_I	16703	16989	98.3
(ng•hr/mL)	17186 (22)	17241 (18)	
C_{max}	1414	1420	99.5
(ng/mL)	1459 (24)	1450 (21)	
T_{max} (hr)	3.0 (0.74)	3.4 (0.61)	--
$t_{1/2}$ (hr)	10.8 (1.59)	10.7 (1.67)	--

*The geometric means are presented for AUC_T, AUC_I and C_{max} parameters
**For T_{max} and $t_{1/2}$ parameters, the arithmetic means (SD) are presented

These results demonstrate the bioequivalence of these two formulations.

INDICATIONS AND CLINICAL USE

No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic 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 antiarrhythmic therapy for all patients with ventricular arrhythmias.

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

For patients with sustained ventricular tachycardia, Sandoz Sotalol 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 Sandoz Sotalol, its use in patients with hypertension or angina pectoris is not recommended unless they also require Sandoz Sotalol for the treatment of ventricular arrhythmias.

CONTRAINDICATIONS

Sandoz 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.

WARNINGS

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 antiarrhythmic agent.

Proarrhythmia: Sandoz 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 Sandoz Sotalol be evaluated clinically and electrocardiographically prior to, and during therapy to determine whether the response to Sandoz Sotalol supports continued treatment. Sotalol hydrochloride, like some antiarrhythmic 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, 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, Sandoz Sotalol is not recommended for the treatment of patients with asymptomatic premature contractions (see INDICATIONS AND CLINICAL USE).

Overall in clinical trials with sotalol, 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 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 torsade de pointes was 1% and 1.4%, respectively.

As shown in the table below, torsade de pointes arrhythmias as well as the prolongation of QT (QT_c) interval were dose related.

Percent Incidence of Torsade de Pointes and Mean QT_c 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 assessed; * 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 QT_c 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%). Of the patients experiencing torsade de pointes, approximately two-thirds spontaneously reverted to their baseline rhythm. The others were either converted electrically (D/C cardioversion or overdrive pacing) or treated with other drugs (see SYMPTOMS AND TREATMENT OF OVERDOSAGE). It is not possible to determine whether some sudden deaths represented episodes of torsade de pointes, but in some instances sudden death did follow a documented episode of torsade de pointes. Although sotalol therapy was discontinued in most patients experiencing torsade de pointes, 17% were continued on a lower dose. Nonetheless, Sandoz Sotalol should be used with particular caution if the QT_c is greater than 500 msec on-therapy and serious consideration should be given to reducing the dose or discontinuing therapy when the QT_c exceeds 550 msec. Due to the multiple risk-factors associated with torsade de pointes, however, caution should be exercised regardless of the QT_c interval. The table below relates the incidence of torsade de pointes to on-therapy QT_c and change in QT_c from baseline. It

should be noted, however, that the highest on-therapy QT_c was in many cases the one obtained at the time of the torsade de pointes event, so that the table overstates the predictive value of a high QT_c.

Relationship Between QT_C 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 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 in patients with diminished renal function, by appropriate dose reduction, should also reduce the risk of proarrhythmia (see DOSAGE AND ADMINISTRATION).

Electrolyte Disturbances: Sandoz 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.

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, Proarrhythmia).

In patients with controlled CHF, Sandoz Sotalol should be administered cautiously. The positive inotropic action of digitalis may be reduced when the two drugs are used concomitantly. Both digitalis and sotalol slow AV conduction. If cardiac failure continues despite adequate digitalization, Sandoz 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 Sandoz 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 Sandoz Sotalol. The incidence 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 (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 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 2^{nd}- or 3^{rd}-degree AV block is approximately 1%.

Recent Myocardial Infarction: Caution should be exercised when Sandoz Sotalol 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), there were four fatalities and three serious hemodynamic/electrical adverse events within two weeks of initiating sotalol hydrochloride.

Abrupt Cessation of Therapy: Patients should be warned against abrupt interruption or discontinuation of Sandoz Sotalol. 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 Sandoz Sotalol, particularly in patients with ischemic heart disease, to carefully monitor the patient and to discontinue Sandoz 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 Sandoz 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.

Non-Allergic Bronchospasm (e.g. Chronic Bronchitis and Emphysema): **Patients with bronchospastic diseases should in general not receive beta-blockers**. It is prudent, if Sandoz 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.

Sick Sinus Syndrome: Sandoz 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.

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.

Thyrotoxicosis: In patients with thyrotoxicosis, Sandoz 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

Sandoz Sotalol which might be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

PRECAUTIONS

Renal Impairment: Renal function tests should be carried out at appropriate intervals. Caution should be observed in patients with impaired renal function since Sandoz 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. Guidance for dosing in conditions of renal impairment can be found under DOSAGE AND ADMINISTRATION.

Diabetes: Sandoz 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 agents. Beta-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia; e.g. tachycardia.

Anesthesia: It is not advisable to withdraw beta-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using Sandoz Sotalol with anesthetic 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 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.

Use in Pregnancy: 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, Sandoz Sotalol should be used during pregnancy only if the potential benefit outweighs the potential risk.

Use in Nursing Mothers: Sotalol has been reported to be present in human milk. Because of the potential for adverse reactions from Sandoz 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.

Use in Children: The safety and effectiveness of Sandoz Sotalol in children have not been established.

Drug Interactions

Antiarrhythmics: Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide, and Class III drugs (e.g. amiodarone) are not recommended as concomitant therapy with Sandoz Sotalol because of their potential to prolong refractoriness (see WARNINGS). There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics. Additive Class II effects would also be anticipated with the use of other beta-blocking agents concomitantly with Sandoz Sotalol.

Drugs Prolonging the QT Interval: Sandoz 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 antiarrhythmics, phenothiazines, tricyclic antidepressants, terfenadine, astemizole, erythromycin, lithium and liquid protein diets.

Digoxin: Single and multiple doses of 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: Sandoz 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 Sandoz 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 drugs should be adjusted accordingly (see 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 Sandoz Sotalol.

ADVERSE REACTIONS

During premarketing 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), 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 therapy but no cause and effect relationship has been established.

One case of peripheral neuropathy which resolved on discontinuation of sotalol 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.

The following table lists as a function of dosage the most common (incidence of 2% or greater) adverse effects, 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.

Incidence (%) of Adverse Events and Discontinuations							
Body System	Daily Dose						
	160 mg (n=832)	240 mg (n=263)	320 mg (n=835)	480 mg (n=459)	640 mg (n=324)	Any Dose* (n=1292)	%Patients Discont. (n=1292)
BODY AS A WHOLE							
Infection	1	2	2	2	3	4	<1
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
Lightheaded	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
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 lab 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 AND 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.

Potential Adverse Effects

Marketing experience with sotalol hydrochloride showed 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 nonthrombocytopenia purpura.

Gastrointestinal: Mesenteric arterial thrombosis; ischemic colitis.

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

SYMPTOMS AND TREATMENT OF 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 sotalol hydrochloride should be discontinued. Close monitoring of the electrocardiogram in patients with suspected sotalol intoxication is

essential. Because of the lack of protein binding, hemodialysis is useful for reducing sotalol 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).

If required, the following therapeutic measures are suggested:

1) Bradycardia: Atropine, another anticholinergic drug, a beta-adrenergic agonist or transvenous cardiac 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 sulphate, transvenous cardiac pacing, DC cardioversion.

It should be remembered that 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 Sandoz Sotalol. However, the complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

Sandoz 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). Sandoz Sotalol should be administered only after appropriate clinical assessment, and the dosage of Sandoz 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.

Dosage of Sandoz 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 sotalol hydrochloride, dosing on more than a twice daily regimen is not usually necessary.

Patients experiencing bradycardia or hypotension on initial administration of Sandoz Sotalol should be removed from therapy; Sandoz 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.

Renal Impairment: Because sotalol 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 Sandoz 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 Sandoz Sotalol: Based on theoretical considerations rather than experimental data, the following suggestion is made: when transferring patients from another antiarrhythmic drug to Sandoz Sotalol or from Sandoz Sotalol to another antiarrhythmic 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 antiarrhythmic agent is likely to produce life-threatening arrhythmias, the physician should consider hospitalizing the patient.

PHARMACEUTICAL INFORMATION

Drug Substance

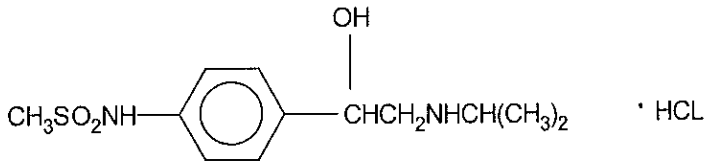
Proper Name: Sotalol hydrochloride

Chemical Name(s):

1) Methanesulfonamide, *N*-[4-[1-hydroxy-2-[(1-methylethyl)-amino]ethyl]phenyl]-, monohydrochloride

2) 4'-[1-Hydroxy-2-(isopropyl-amino)ethyl]-methane-sulfonanilide monohydrochloride

Structural Formula:



Molecular Formula: $C_{12}H_{20}N_2O_3S \cdot HCl$

Molecular Weight: 308.82

Description: Sotalol hydrochloride is a white to pale cream, crystalline, odourless powder which has a melting point of 212 - 214°C. It is freely soluble in water and methanol, and sparingly soluble in chloroform.

Composition

The non-medicinal ingredients in Sandoz Sotalol are colloidal silicon dioxide, dextrates, indigotine (Blue #2), magnesium stearate and methylcellulose.

Stability and Storage Recommendations

Store at room temperature (15 to 30°C). Protect from light.

AVAILABILITY OF DOSAGE FORMS

Each blue, capsule-shaped, biconvex tablet, identified "RXP-80" on one side and scored on the other, contains 80 mg of sotalol hydrochloride. Available in bottles of 100, 250, 500 and 1000.

Each blue, capsule-shaped, biconvex tablet, identified "RXP-160" on one side and scored on the other, contains 160 mg of sotalol hydrochloride. Available in bottles of 100, 250, 500 and 1000.

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, and 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 does not alter intraocular pressure.

TOXICOLOGY

Acute Toxicity

Species	Sex	No. of Animals	Route	LD_{50} (mg/kg)	No. of Deaths
Mice	M	50	Oral	2600	15
	M	130	i.p.	670	36
				645	
	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; LD_{50} could not be determined					

Signs of toxicity were: ataxia, labored respiration, loss of righting reflex, depression, hypoactivity, asphyxial movements and 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 nictitating membrane, moderate tearing, watery stools, weak heart beat, profuse salivation, coarse tremors and piloerection.

Chronic Toxicity

Species	Sex	Route of Administration	Dosage Regimen	Time Period	Toxicity Signs
Mice	F	Oral	500 mg/ kg/day	6 months	None
Rats	M&F	Oral	0,50,250, 1250 mg/ kg/day	1 year	Ataxia, depression, slightly depressed growth and food efficiency, increased spleen weight
Rats	M&F	Oral	0,75,275, 975 or 1000 mg/ kg/day	1 year	Decrease in body weight gain (dose-related), increases in heart dimensions of male rats and cartilagenous metaplasia in heart sections
Dogs	M&F	Oral	0,5,15,45, 60 or 70 mg/kg/day	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 and 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 teratogenesis 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 resorptions, 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 tumours 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.

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