HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use sotalol hydrochloride injection safely and effectively. See full prescribing information for sotalol hydrochloride injection.

SOTALOL hydrochloride injection for intravenous use
Initial U.S. Approval: 1992

WARNING: LIFE THREATENING PROARRHYTHMIA

See full prescribing information for complete boxed warning.

- **Sotalol can cause life threatening ventricular tachycardia associated with QT interval prolongation.**
- **Do not initiate sotalol therapy if the baseline QTc is longer than 450 ms. If the QT interval prolongs to 500 ms or greater, the dose must be reduced, the duration of the infusion prolonged or the drug discontinued.**
- **Patient should be hospitalized in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring.**
- **Adjust the dosing interval based on creatinine clearance.**

INDICATIONS AND USAGE

Sotalol hydrochloride for intravenous use is an antiarrhythmic agent indicated for:

- Substitution for oral sotalol in patients who are unable to take sotalol orally (1.1)

Oral sotalol is indicated for:

- Maintenance of normal sinus rhythm in patients with history of highly symptomatic atrial fibrillation/flutter (1.2)
- Treatment of documented life-threatening ventricular arrhythmias (1.3)

DOSAGE AND ADMINISTRATION

Intravenous sotalol must be diluted. Appropriate diluents are saline, 5% dextrose in water (D5W), or Ringer's lactate. Intravenous sotalol is administered by a volumetric infusion pump over 5 hours at a constant infusion rate. See full prescribing information for general rules and safety measures (2.1), dose selection (2.2) and preparation of infusion (2.3)

Maintenance of sotalol therapy – Replacement of Oral Dosing

The intravenous dose is approximately equal to the oral dose and administered at the same dosing frequency. 75 mg of intravenous sotalol is approximately equal to 80 mg of oral sotalol (2.2)

Initiation of Therapy

- Calculate creatinine clearance to determine dosing interval (2.1).
- Starting adult dose is 75 mg administered twice daily. If creatinine clearance is between 60 and 40 mL/min, administer once daily, if less than 40 mg/mL, sotalol is not recommended (2.1).
- The dose can be up-titrated to maximal dose of 150 mg twice daily under close ECG and QT interval monitoring (2.5, 2.6)

DOSAGE FORMS AND STRENGTHS

- 150 mg sotalol hydrochloride in 10 mL vial (15 mg/mL) (Must be diluted prior to use)

CONTRAINDICATIONS

- Sinus bradycardia (<50 bpm), sick sinus syndrome or 2nd and 3rd degree AV block unless a functioning pacemaker is present (4)
- Congenital or acquired long QT syndromes, QT interval >450 ms (4)
- Cardiogenic shock, uncontrolled heart failure (4)
- Creatinine clearance <40 mL/min (4)
- Serum potassium <4 meq/L (4)
- Bronchial asthma or related bronchospastic conditions (4)
- Known hypersensitivity to sotalol (4)

WARNINGS AND PRECAUTIONS

- QT prolongation and proarrhythmia: Reduce dose, reduce rate of infusion, or discontinue (5.1)
- Bradycardia, AV block, hypotension, worsening heart failure: Reduce dose as needed (5.3, 5.4, 5.5. 5.6)
- Acute exacerbation of coronary artery disease upon cessation of therapy: Do not abruptly discontinue (5.8)
- Electrolyte disturbances must be corrected (5.9)
- Monitor serum glucose in diabetic patients as sotalol may mask symptoms of hypoglycemia, or worsen hyperglycemia (5.12)

ADVERSE REACTIONS

Most common adverse reactions (>10%) seen with oral sotalol (dose related) are fatigue, dizziness, lightheadedness, headache, asthenia, nausea, dyspnea, bradycardia, chest pain, and palpitation (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Altathera Pharmaceuticals LLC at 1-800-524-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Digoxin increases the risk of proarrhythmic events (7.1)
- Calcium blocking drugs may have additive effects on decreasing atrioventricular conduction, ventricular function, and blood pressure (7.2)
- Concomitant use of catecholamine-depleting drugs may produce hypotension, marked bradycardia, and syncope (7.3)
- Dosage of insulin or antidiabetic drugs may require adjustment (hyperglycemia). Symptoms of hypoglycemia may be masked (7.4)
- Dose of beta-2 receptor agonists may have to be increased (7.5)
- Sotalol may potentiate the rebound hypertension after discontinuation of clonidine (7.6)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Sotalol is excreted in milk in large amounts; potential harm to the infants. Discontinue nursing or discontinue the drug (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: November 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE THREATENING PROARRHYTHMIA

To minimize the risk of induced arrhythmia, patients initiated or re-initiated on intravenous sotalol, and patients who are converted from intravenous to oral administration should be hospitalized in a facility that can provide cardiac resuscitation, continuous electrocardiographic monitoring and calculations of creatinine clearance.

- **Sotalol can cause life threatening ventricular tachycardia associated with QT interval prolongation**
- **Do not initiate sotalol therapy if the baseline QTc is longer than 450 ms. If the QT interval prolongs to 500 ms or greater, the dose must be reduced, the duration of the infusion prolonged or the drug discontinued**
- **Adjust the dosing interval based on creatinine clearance**

1 INDICATIONS AND USAGE

1.1 Substitution for Oral Sotalol Therapy

Intravenous sotalol can substitute for oral sotalol in patients who are unable to take sotalol orally.

1.2 Delay in Recurrence of Atrial Fibrillation/Atrial Flutter

Sotalol is indicated for the maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. Because sotalol can cause life-threatening ventricular arrhythmias, it should be reserved for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL is easily reversed (by Valsalva maneuver, for example) should usually not be given sotalol. In general, antiarrhythmic therapy for AFIB/AFL aims to prolong the time in normal sinus rhythm. Recurrence is expected in some patients *[see Clinical Studies (14.2)]*.

Patients with atrial fibrillation should be anticoagulated according to usual medical practice.

1.3 Documented Life-Threatening Ventricular Arrhythmia

Sotalol is indicated for the treatment of documented life-threatening ventricular arrhythmias. Because of the proarrhythmic effects of sotalol *[see Warnings and Precautions (5.1)]* including a 1.5 to 2% rate of Torsade de Pointes or new VT/VF in patients with either NSVT or supraventricular arrhythmias, its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided. In life-threatening ventricular arrhythmias, the response to treatment should then be evaluated by a suitable method (e.g., PES or Holter monitoring) at steady state blood levels of drug prior to continuing the patient on chronic therapy. Antiarrhythmic drugs may not enhance survival in patients with ventricular arrhythmias.

2 DOSAGE AND ADMINISTRATION

2.1 General Rules and Safety Measures of Intravenous Sotalol Therapy

For the safety of the patient, the safety measures required of oral sotalol administration must also be applied for intravenous route. To minimize the risk of induced arrhythmia, patients initiated or re-initiated on sotalol should be hospitalized for at least three days or until steady state drug levels are achieved, in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Initiate intravenous sotalol therapy in the presence of personnel trained in the management of serious ventricular arrhythmias. Perform a baseline ECG to determine the QT interval and measure and normalize serum potassium and magnesium levels before initiating therapy with starting sotalol injection. Measure serum creatinine and calculate an estimated creatinine clearance in order to establish the appropriate dosing interval for sotalol.

If the baseline QT is greater than 450 ms (JT >330 ms if QRS over 100 ms), sotalol is not recommended.

The patient's creatinine clearance should be calculated using the one of several formulas. The Cockcroft-Gault formula to determine creatinine clearance is:

$$\text{Creatinine clearance (male)} = \frac{(140\text{-age}) \times \text{body weight in kg}}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Creatinine clearance (female)} = \frac{(140\text{-age}) \times \text{body weight in kg} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

When serum creatinine is given in µmol/L, divide the value by 88.4 (1 mg/dL = 88.4 µmol/L).

Start sotalol therapy only if the baseline QT interval is <450 ms. During initiation and titration, monitor the QT interval after the completion of each infusion If the QT interval prolongs to 500 ms or greater, reduce the dose, decrease the infusion rate, or discontinue the drug.

Administer sotalol twice daily in patients with a creatinine clearance >60 mL/min or once daily) in patients with a creatinine clearance between 40 and 60 mL/min. Sotalol is not recommended in patients with a creatinine clearance <40 mL/min. The recommended initial IV dose of sotalol is 75 mg (once or twice daily) and is initiated as shown in the dosing algorithm described below. The 75 mg dose can be titrated upward to 112.5 or 150 mg after at least 3 days *[see Dosage and Administration (2.5)]*.

2.2 Dose of Intravenous Sotalol

The bioavailability of oral sotalol is between 90% and 100%. The corresponding dose of intravenous sotalol is, therefore, slightly less than that of the oral dose. The effects of the initial intravenous dose must be monitored and the dose titrated either upward or downward, if needed, based on clinical effect, QT interval, or adverse reactions.

Table 1: Conversion from Oral Sotalol to Intravenous Sotalol

Oral dose Once or twice daily	Intravenous dose Once or twice daily Administered over 5 hours
80 mg	75 mg (5 mL sotalol injection)
120 mg	112.5 mg (7.5 mL sotalol injection)
160 mg	150 mg (10 mL sotalol injection)

2.3 Preparation of Sotalol Infusion

Intravenous sotalol must be diluted for infusion. Appropriate diluents are saline, 5% dextrose in water (D5W), or Ringer's lactate. Usually, prepare in a volume of 100-250 mL. Use a volumetric infusion pump to infuse intravenous sotalol at a constant rate. The following table compensates for dead space in the infusion set.

Table 2: Sotalol Infusion Preparation to Compensate for Dead Space in Infusion Set

Target Dose	Sotalol Injection	Diluent	Volume Prepared	Volume to Infuse
75 mg	6 mL	114 mL	120 mL	100 mL
112.5 mg	9 mL	111 mL		100 mL
150 mg	12 mL	108 mL		100 mL
75 mg	6 mL	294 mL	300 mL	250 mL
112.5 mg	9 mL	291 mL		250 mL
150 mg	12 mL	288 mL		250 mL

2.4 Initiation of Intravenous Sotalol Therapy

The starting dose of intravenous sotalol is 75 mg infused over 5 hours once or twice daily based on the creatinine clearance. Monitor ECG for excessive increase in QTc.

2.5 Upward Titration of Dose

If the 75 mg dose of intravenous sotalol does not reduce the frequency of relapses of life threatening ventricular arrhythmias or symptomatic AFIB/AFL and is tolerated without excessive (i.e., to >500 ms) QTc prolongation, increase the dose to 112.5 mg infused over 5 hours, once or twice daily depending upon the creatinine clearance. Continue to monitor QTc during dose escalations.

2.6 Dose for Ventricular Arrhythmias

The recommended initial dose of intravenous sotalol is 75 mg infused over 5 hours, once or twice daily based on creatinine clearance. The dose may be increased in increments of 75 mg/day every 3 days. The usual therapeutic effect is observed with oral doses of 80 to 160 mg once or twice a day (corresponding to 75 to 150 mg intravenous sotalol). Oral doses as high as 240-320 mg once or twice a day (corresponding to 225 to 300 mg intravenous sotalol) have been utilized in patients with refractory life-threatening arrhythmias.

2.7 Dose for Symptomatic AFIB/AFL

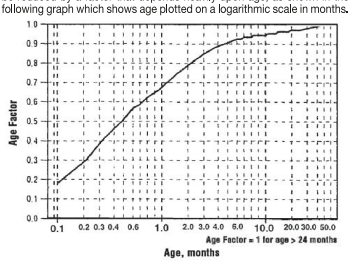
In the U.S. multicenter dose-response study, 120 mg orally once or twice a day (corresponding to 112.5 mg intravenous sotalol) was found to be the most effective dose in prolonging the time to ECG-documented symptomatic recurrence of AFIB/AFL. If that dose level, at steady state, does not reduce the frequency of early relapse of arrhythmia and is tolerated without excessive QTc prolongation (>520 ms), increase the dose to 160 mg orally once or twice a day (corresponding to 150 mg intravenous sotalol).

2.8 Dosing and Administration in Children

Intravenous sotalol has not been studied in children. As in adults the following precautionary measures should be considered when initiating sotalol treatment in children: initiation of treatment in the hospital after appropriate clinical assessment; individualized regimen as appropriate; gradual increase of doses if required; careful assessment of therapeutic response and tolerability; and frequent monitoring of the QTc interval and heart rate.

For children aged about 2 years and greater, with normal renal function, doses normalized for body surface area are appropriate for both initial and incremental dosing. Since the Class III potency in children *[see Clinical Pharmacology (12.2)]* is not very different from that in adults, reaching plasma concentrations that occur within the adult dose range is an appropriate guide. From pediatric pharmacokinetic data the following is recommended. For initiation of treatment, 30 mg/m^2 three times a day (90 mg/m^2 total daily dose) is approximately equivalent to the initial 160 mg total oral daily dose for adults. Subsequent titration to a maximum of 60 mg/m^2 (approximately equivalent to the 360 mg total daily dose for adults) can then occur. Titration should be guided by clinical response, heart rate and QTc, with increased dosing being carried out in-hospital. At least 36 hours should be allowed between dose increments to attain steady-state plasma concentrations of sotalol in patients with age-adjusted normal renal function.

For children about 2 years or younger the above pediatric dosage should be reduced by a factor that depends heavily upon age, as shown in the following graph which shows age plotted on a logarithmic scale in months.



For a child aged 20 months, the dosing suggested for children with normal renal function aged 2 years or greater should be multiplied by about 0.97; the initial starting dose would be (30 × 0.97) = 29.1 mg/m^2, administered orally three times daily. For a child aged 1 month, the starting dose should be multiplied by 0.68; the initial starting dose would be (30 × 0.68) = 20 mg/m^2, administered orally three times daily. For a child aged 1 week, the initial starting oral dose should be multiplied by 0.3; the starting dose would be (30 × 0.3) = 9 mg/m^2. Similar calculations should be made for increased doses as titration proceeds. Since the half-life of sotalol decreases with decreasing age (below about 2 years), time to steady-state will also increase. Thus, in neonates the time to steady-state may be as long as a week or longer.

In all children, individualization of dosage is required. As in adults sotalol should be used with particular caution in children if the QTc is greater than 500 ms on therapy and serious consideration should be given to reducing the dose or discontinuing therapy when QTc exceeds 550 ms.

The use of oral sotalol in children with renal impairment has not been investigated. Sotalol elimination is predominantly via the kidney in the unchanged form. Use of sotalol in any age group with decreased renal function should be at lower doses or at increased intervals between doses. Monitoring of heart rate and QTc is most important. It will take much longer to reach steady-state with any dose and/or frequency of administration in these children.

3 DOSAGE FORMS AND STRENGTHS

150 mg sotalol hydrochloride in 10 mL vial (15 mg/mL).

4 CONTRAINDICATIONS

- Sinus bradycardia (<50 bpm), sick sinus syndrome or second or third degree AV block unless a functioning pacemaker is present
- Congenital or acquired long QT syndromes, QT interval >450 ms
- Cardiogenic shock, uncontrolled heart failure
- Creatinine clearance <40 mL/min
- Serum potassium <4 meq/L
- Bronchial asthma or related bronchospastic conditions
- Known hypersensitivity to sotalol

5 WARNINGS AND PRECAUTIONS

5.1 QT Prolongation and Proarrhythmia

Sotalol can cause serious ventricular arrhythmias, primarily Torsade de Pointes (TdP) type ventricular tachycardia, a polymorphic ventricular tachycardia associated with QTc prolongation. QTc prolongation is directly related to the concentration of sotalol. Factors such as reduced creatinine clearance, gender (female) and larger doses increase the risk of TdP. The risk of TdP can be reduced by adjustment of the sotalol dose according to creatinine clearance and by monitoring the ECG for excessive increases in QTc.

Initiate sotalol only in a facility that can provide ECG monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias. Steady-state plasma levels of sotalol and maximum QTc prolongation occur by 3 days. Calculation of the creatinine clearance must precede administration of the first dose of sotalol. For detailed instructions regarding dose selection *[see Dosage and Administration (2)]*.

5.2 Use with Drugs that Prolong QT Interval and Antiarrhythmic Agents

The use of sotalol in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended. Such drugs include many antiarrhythmics, some phenothiazines, tricyclic antidepressants, and certain oral macrolides. Class I or Class III antiarrhythmic agents should be withheld for at least three half-lives prior to dosing with sotalol. In clinical trials, sotalol was not administered to patients previously treated with oral amiodarone for >1 month in the previous three months. Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other Class III drugs (e.g., amiodarone) are not recommended as concomitant therapy with intravenous sotalol because of their potential to prolong refractoriness. There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics.

5.3 Bradycardia/Heart Block

In studies of oral sotalol, the incidence of bradycardia (as determined by the investigators) in the supraventricular arrhythmia population treated with oral sotalol was 13% and led to discontinuation in 2.4%. Bradycardia itself increases the risk of Torsade de Pointes, so carefully monitor patients receiving concomitant digoxin.

5.4 Sick Sinus Syndrome

In general, sotalol is not recommended in patients with sick sinus syndrome associated with symptomatic arrhythmias, because it may cause sinus bradycardia, sinus pauses, or sinus arrest. In patients with AFIB and sinus node dysfunction, sotalol increases the risk of Torsade de Pointes, especially after cardioversion. Sotalol augments bradycardia and QTc prolongation following cardioversion. Patients with AFIB/AFL associated with the sick sinus syndrome may be treated with sotalol if they have an implanted pacemaker for control of bradycardia symptoms.

5.5 Hypotension

Sotalol produces significant reductions in both systolic and diastolic blood pressures and may result in hypotension. Although sotalol is usually well-tolerated, monitor hemodynamics in patients with marginal cardiac compensation as deterioration in cardiac performance may occur.

5.6 Heart Failure

Sympathetic stimulation is necessary in supporting circulatory function in heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In a pooled data base of four placebo-controlled AFIB/AFL and PSVT studies, new or worsening heart failure occurred during therapy with oral sotalol in 5 (1.2%) of 415 patients. In these studies patients with uncontrolled heart failure were excluded (i.e., NYHA Functional Classes III or IV).

In other premarketing oral sotalol studies, new or worsened heart failure occurred in 3% of patients and led to discontinuation in approximately 1% of patients receiving sotalol. The incidence was higher in patients presenting with sustained ventricular tachycardia/fibrillation (5%), or a prior history of heart failure (7%). Based on a life-table analysis, the one-year incidence of new or worsened heart failure was 3% in patients without a prior history and 10% in patients with a prior history of heart failure.

5.7 Recent Acute MI

Oral sotalol has been used in a controlled trial following an acute myocardial infarction without evidence of increased mortality *[see Clinical Studies (14.3)]*. Although specific studies of its use in treating atrial arrhythmias after infarction have not been conducted, the usual precautions regarding heart failure, avoidance of hypokalemia, bradycardia or prolonged QT interval apply. Experience in the use of sotalol to treat ventricular arrhythmias in the early phase of recovery from acute MI is limited. In the first 2 weeks post-MI careful dose titration is especially important, particularly in patients with markedly impaired ventricular function.

5.8 Abrupt Withdrawal

Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias and, in some cases, myocardial infarction have been reported after abrupt discontinuation of beta-blocker therapy. Therefore, when discontinuing chronically administered sotalol, particularly in patients with ischemic heart disease, carefully monitor the patient and consider the temporary use of an alternative beta-blocker if appropriate. If possible, the dosage of sotalol should be gradually reduced over a period of one to two weeks. If angina or acute coronary insufficiency develops, appropriate therapy should be instituted promptly. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized in patients receiving sotalol, abrupt discontinuation in patients with arrhythmias may unmask latent coronary insufficiency.

5.9 Electrolyte Disturbances

Sotalol should not be used in patients with hypokalemia or hypomagnesemia prior to correction of imbalance, as these conditions increase the potential for Torsade de Pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or patients receiving concomitant diuretic drugs.

5.10 Renal Impairment

Sotalol is eliminated principally 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 *[see Dosage and Administration (2)]*.

5.11 Non-Allergic Bronchospasm

Patients with bronchospastic diseases should, in general, not receive beta-blockers. If sotalol is to be administered, use the smallest effective dose, to minimize inhibition of bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

5.12 Diabetes

Beta-blockade may mask some important premonitory signs of acute hypoglycemia (e.g., tachycardia) in patients with diabetes (especially labile diabetes) or with a history of episodes of spontaneous hypoglycemia.

5.13 Thyrotoxicosis

Beta-blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Avoid abrupt withdrawal of beta-blockade which might be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. The beta-blocking effects of sotalol may be useful in controlling heart rate in AFIB associated with thyrotoxicosis, but no study has been conducted to evaluate this.

5.14 Anaphylaxis

While taking beta-blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

5.15 Anesthesia

The management of patients undergoing major surgery who are being treated with beta-blockers is controversial. Protracted severe hypotension and difficulty in restoring and maintaining normal cardiac rhythm after anesthesia have been reported in patients receiving beta-blockers.

5.16 Drug/Laboratory Test Interactions

The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by fluorimetric or photometric methods.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

There is no clinical experience with intravenous sotalol. However, because of the similarity of exposure with intravenous sotalol and oral sotalol, the adverse reactions should be similar.

Adverse reactions that are clearly related to sotalol are those which are typical of its Class II (beta-blocking) and Class III (cardiac action potential duration prolongation) effects. The common documented beta-blocking adverse reactions (bradycardia, dyspnea, and fatigue) and Class III effects (QT interval prolongation) are dose related.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Serious Adverse Reactions

Sotalol can cause serious ventricular arrhythmias, primarily Torsade de Pointes (TdP) type ventricular tachycardia, a polymorphic ventricular tachycardia associated with QT interval prolongation. QT interval prolongation is directly related to the plasma level of sotalol. Factors such as reduced creatinine clearance, gender (female) and larger doses increase the risk of TdP *[see Warning and Precautions (5.1)]*.

Proarrhythmia in Atrial Fibrillation Patients: In eight controlled trials of patients with AFIB/AFL and other supraventricular arrhythmias (N=659) there were four cases of TdP reported (0.6%) during the controlled phase of treatment with oral sotalol.

Prolongation of the QT interval is dose related, increasing from baseline an average of 25, 40, and 50 ms in the 80, 120, and 160 mg groups, respectively, in the oral dose-response study.

Proarrhythmia in Ventricular Arrhythmia Patients: In patients with a history of sustained ventricular tachycardia, the incidence of Torsade de Pointes during oral sotalol treatment was 4% and worsened VT was about 1%; in patients with other less serious ventricular arrhythmias the incidence of Torsade de Pointes was 1% and new or worsened VT was about 0.7%. 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. Torsade de Pointes arrhythmias in patients with VT/VF were dose related, as was the prolongation of QT (QTc) interval, as shown in Table 1 below.

Table 1: Percentage Incidence of Torsade de Pointes and Mean QTc Interval by Oral Dose for Patients with Sustained VT/VF

Daily Dose [mg]	Incidence of Torsade de Pointes	Mean QTc * [ms]
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

Table 2 below relates the incidence of Torsade de Pointes to on-therapy QTc and change in QTc from baseline. It should be noted, however, that the highest on-therapy QTc 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 QTc.

Table 2: Relationship Between QTc Interval Prolongation and Torsade de Pointes

On-Therapy QTc Interval [ms]	Incidence of Torsade de Pointes	Change in QTc Interval From Baseline [ms]	Incidence of Torsade de Pointes
less than 500	1.3% (1787)	less than 65	1.6% (1516)
500-525	3.4% (236)	65-80	3.2% (158)
525-550	5.6% (125)	80-100	4.1% (146)
>550	10.8% (157)	100-130	5.2% (115)
		>130	7.1% (99)

( ) Number of patients assessed

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 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 ventricular arrhythmia 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 Overdosage (10)]*. 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, intravenous sotalol should be used with particular caution if the QTc is greater than 500 ms on-therapy and serious consideration should be given to reducing the dose or discontinuing therapy when the QTc exceeds 520 ms. Proarrhythmic events must be anticipated not only on initiating therapy, but with every upward dose adjustment.

Other Adverse Reactions

No data are available with intravenous sotalol. In a pooled clinical trial population consisting of four placebo-controlled studies with 275 patients with AFIB/AFL treated with 160-320 mg doses of oral sotalol the following adverse events were reported at a rate of 2% or more in the 160-240 mg treated patients and greater than the rate in placebo patients (See Table 3). The data are presented by incidence of events in the sotalol and placebo groups by body system and daily dose. No significant irreversible non-cardiac end-organ toxicity was observed.

Table 3: Incidence (%) of Common Adverse Reactions (≥2% in the 160-240 mg group and more frequent than on placebo) in Four Placebo-Controlled Studies of Patients with AFIB/AFL Treated with Oral Sotalol

	Placebo	Sotalol Total Daily Dose	
Body System/ Adverse Reactions (Preferred Term)	N=282	160-240 N=153	>240-320 N=122
CARDIOVASCULAR			
Bradycardia	2.5	13.1	12.3
Disturbance Rhythm Subjective	9.9	9.8	7.4
Abnormality ECG	0.4	3.3	2.5
Chest Pain Cardiac/Non-Anginal	4.6	4.6	2.5
Angina Pectoris	1.1	2.0	1.6
Disturbance Rhythm Atrial	2.1	2.0	1.6
GASTROINTESTINAL			
Diarrhea	2.1	5.2	5.7
Nausea/Vomiting	5.3	7.8	5.7
Distention Abdomen	0.4	0.7	2.5
Dyspepsia/Heartburn	1.8	2.0	2.5
Pain Abdomen	2.5	3.9	2.5
Appetite Decreased	0.4	2.0	1.6
GENERAL			
Fatigue	8.5	19.6	18.9
Hyperhidrosis	3.2	5.2	4.9
Weakness	3.2	5.2	4.9
Fever	0.7	0.7	3.3
Sensation Cold	0.7	2.0	2.5
Influenza	0.4	2.0	0.8
MUSCULOSKELETAL/CONNECTIVE TISSUE			
Pain Musculoskeletal	2.8	2.6	4.1
Pain Chest Musculoskeletal	1.4	2.0	2.5
NERVOUS SYSTEM			
Dizziness	12.4	16.3	13.1
Headache	5.3	3.3	11.5
Insomnia	1.1	2.6	4.1
RESPIRATORY			
Dyspnea	7.4	9.2	9.8
Infection Upper Respiratory	1.1	2.6	3.3
Tracheobronchitis	0.7	0.7	3.3
Cough	2.5	3.3	2.5
SPECIAL SENSES			
Disturbance Vision	0.7	2.6	0.8

Overall, discontinuation because of unacceptable adverse events was

necessary in 17% of the patients, and occurred in 10% of patients less than two weeks after starting treatment. The most common adverse events leading to discontinuation of sotalol were: fatigue 4.6%, bradycardia 2.4%, proarrhythmia 2.2%, dyspnea 2%, and QT interval prolongation 1.4%.

In clinical trials involving 1292 patients with sustained VT/VF, the common adverse events (occurring in ≥2% of patients) were similar to those described for the AFIB/AFL population. Table 4 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 4: Incidence (%) of Adverse Events and Discontinuations (Disc) in 1292 patients with sustained VT/VF Receiving Oral Sotalol Therapy

	Daily Dose						% Disc
	160 mg	240 mg	320 mg	480 mg	640 mg	Any Dose*	
Body System	n=832	n=263	n=835	n=459	n=324	n=1292	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 (CV)							
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
Periph vascular	1	2	1	1	2	3	<1
CV 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
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 resp. 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
Sex. dysfunction	<1	1	1	1	3	2	<1
METABOLIC							
Abnormal lab	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.

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.

Pediatrics

There are no studies of intravenous sotalol in pediatric patients. In an unblinded multicenter trial of 25 pediatric patients with SVT and/or VT receiving daily oral doses of 30, 90 and 210 mg/m^2 with dosing every 8 hours for a total of 9 doses, no Torsade de Pointes or other serious new arrhythmias were observed. One (1) patient, receiving 30 mg/m^2 daily, was discontinued because of increased frequency of sinus pauses/bradycardia. Additional cardiovascular AEs were seen at the 90 and 210 mg/m^2 daily dose levels. They included QT prolongations (2 patients), sinus pauses/bradycardia (1 patient), increased severity of atrial flutter and reported chest pain (1 patient). Values for QTc ≥525 ms were seen in 2 patients at the 210 mg/m^2 daily dose level. Serious adverse events including death, Torsade de Pointes, other proarrhythmias, high-degree A-V blocks, and bradycardia have been reported in infants and/or children.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of sotalol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency of reporting, or strength of causal connection to the drug.

Postmarketing experience with sotalol shows an adverse reaction profile similar to that described above from clinical trials. Voluntary reports since introduction also include rare reports of: emotional liability, slightly clouded sensorium, incoordination, vertigo, paralysis, thrombocytopenia, eosinophilia, leukopenia, photosensitivity reaction, fever, pulmonary edema, hyperlipidemia, myalgia, pruritis, and alopecia.

Foreign postmarketing experience with intravenous sotalol shows an adverse reaction profile similar to that described above from clinical trials. Sotalol related cardiovascular adverse events occurring in 1% or more of the patients are bradycardia, dyspnea, chest pain, palpitations, edema, ECG abnormalities, hypotension, proarrhythmia, syncope, heart failure, and presyncope.

7 DRUG INTERACTIONS

7.1 Digoxin

Proarrhythmic events were more common in sotalol treated patients also receiving digoxin; it is not clear whether this represents an interaction or is related to the presence of heart failure, a known risk factor for proarrhythmia, in the patients receiving digoxin.

7.2 Calcium Blocking Drugs

Sotalol and calcium blocking drugs can be expected to have additive effects on atrioventricular conduction, ventricular function, and blood pressure.

7.3 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. Monitor such patients for hypotension and marked bradycardia which may produce syncope.

7.4 Insulin and Oral Antidiabetic Agents

Hyperglycemia may occur, and the dosage of insulin or antidiabetic drugs may require adjustment. Symptoms of hypoglycemia may be masked.

7.5 Beta-2-Receptor Stimulants

Beta-agonists such as albuterol, terbutaline and isoproterenol may have to be administered in increased dosages when used concomitantly with sotalol.

7.6 Clonidine

Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine.

7.7 Drugs that Prolong QT Interval and Antiarrhythmic Agents

Sotalol has not been studied with other drugs that prolong the QT interval, such as antiarrhythmics, some phenothiazines, tricyclic antidepressants, and certain oral macrolides. Class I or Class III antiarrhythmic agents should be withheld for at least three half-lives prior to dosing with sotalol. In clinical trials, sotalol was not administered to patients previously treated with oral amiodarone for >1 month in the previous three months. Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other Class III drugs (e.g., amiodarone) are not recommended as concomitant therapy with intravenous sotalol because of their potential to prolong refractoriness *[see Warnings and Precautions (5)]*. There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics.

7.8 Other

No pharmacokinetic interactions were observed with hydrochlorothiazide or warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Sotalol crosses the placenta. In animal studies there was no increase in congenital anomalies, but an increase in early resorptions occurred at sotalol doses 18 times the maximum recommended human dose (MRHD, based on body surface area). Because, animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Reproduction studies in rats and rabbits during organogenesis at sotalol doses 9 and 7 times the MRHD (based on body surface area), respectively, did not reveal any increase in congenital abnormalities. In rabbits, a sotalol dose 6 times the MRHD produced a slight increase in fetal death, but this was associated with maternal toxicity. This effect did not occur at a sotalol dose 3 times the MRHD. In rats, a sotalol dose 18 times the MRHD increased the number of early resorptions, while a dose 2.5 times the MRHD produced no increase in early resorptions.

8.3 Nursing Mothers

Sotalol is secreted in human milk in high levels. In five mothers whose mean sotalol dose was 433 mg/day, sotalol concentrations in milk ranged from 4.8 to 20.2 mg/L (mean=10.5 mg/L), with a milk:plasma ratio of 5.5:1 (range 2.2–8.8). The calculated infant dose was 0.8–3.4 mg/kg, which is similar to recommended therapeutic doses in neonates. Two other case reports showed similar findings. Because of the potential for adverse reactions in nursing infants from sotalol, 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.

8.4 Pediatric Use

The safety and effectiveness of sotalol in children have not been established. However, the Class III electrophysiologic and beta-blocking effects, the pharmacokinetics, and the relationship between the effects (QTc interval and resting heart rate) and drug concentrations have been evaluated in children aged between 3 days and 12 years old *[see Clinical Pharmacology (12)]*.

10 OVERDOSAGE

Intentional or accidental overdosage with sotalol has resulted in death.

Symptoms and Treatment of Overdosage: 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) of sotalol the following clinical findings were seen: hypotension, bradycardia, cardiac asystole, prolongation of QT interval, Torsade de Pointes, ventricular tachycardia, and premature ventricular complexes. If overdosage occurs, therapy with sotalol should be discontinued and the patient observed closely. Because of the lack of protein binding, hemodialysis is useful for reducing sotalol plasma concentrations. Patients should be carefully observed until QT intervals are normalized and the heart rate returns to levels >50 bpm. The occurrence of hypotension following an overdose may be associated with an initial slow drug elimination phase (half life of 30 hours) thought to be due to a temporary reduction of renal function caused by the hypotension.

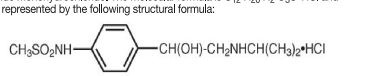
In addition, if required, the following therapeutic measures are suggested:

Bradycardia or Cardiac Asystole:	Atropine, another anticholinergic drug, a beta-adrenergic agonist or transvenous cardiac pacing.
Heart Block:	(second and third degree) transvenous cardiac pacemaker.
Hypotension:	(depending on associated factors) epinephrine rather than isoproterenol or norepinephrine may be useful.
Bronchospasm:	Aminophylline or aerosol beta-2-receptor stimulant.
Torsade de Pointes:	DC cardioversion, magnesium sulfate, potassium replacement. Once Torsade de Pointes is terminated, transvenous cardiac pacing or an isoproterenol infusion to increase heart rate can be employed.

11 DESCRIPTION

Sotalol hydrochloride for injection is an aqueous formulation of sotalol hydrochloride for intravenous use. Sotalol is an antiarrhythmic drug with Class II (beta-adrenoreceptor blocking) and Class III (cardiac action potential duration prolongation) properties.

Intravenous sotalol is supplied as a sterile, clear solution in a 10 mL vial, for intravenous administration after dilution. Each vial contains 150 mg racemic sotalol hydrochloride in sodium acetate buffer. The sotalol hydrochloride concentration of the formulation is 15 mg/mL. Each mL contains 2.9 mg glacial acetic acid in water for injection as an inactive ingredient. The pH of the injection is adjusted with sodium hydroxide to be between 6.0 and 7.0. Sotalol hydrochloride is a white, crystalline solid with a molecular weight of 308.8. It is hydrophilic, soluble in water, propylene glycol and ethanol, but is only slightly soluble in chloroform. Chemically, sotalol hydrochloride is d,l- *N* -[4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]phenyl]methane-sulfonamide monohydrochloride. The molecular formula is $C_{12}H_{20}N_2O_3S$•HCl and is represented by the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Intravenous sotalol 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. The beta-blocking effect of sotalol is non-cardioselective, half maximal at oral doses of about 80 mg/day and maximal at oral doses between 320 and 640 mg/day. Sotalol does not have partial agonist or membrane stabilizing activity. Although significant beta-blockade occurs at oral doses as low as 25 mg, significant Class III effects are seen only at daily doses of 160 mg and above.

In children, a Class III electrophysiological effect can be seen at daily doses of 210 mg/m^2 body surface area (BSA). A reduction of the resting heart rate due to the beta-blocking effect of sotalol is observed at daily doses ≥90 mg/m^2 in children.

12.2 Pharmacodynamics

Electrophysiology: Sotalol prolongs the plateau phase of the cardiac action potential in the isolated myocyte, as well as in isolated tissue preparations of ventricular or atrial muscle (Class II activity). In intact animals it slows heart rate, decreases AV 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 (slowed heart rate), 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 atrio-ventricular 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 ms in QT and 10-40 ms in QTc. In a study of patients with atrial fibrillation /flutter (AFIB/AFL) receiving three different oral doses of sotalol given q12h (or q24h in patients with a reduced creatinine clearance), mean increases in QT intervals measured from 12-lead ECGs of 25 ms, 40 ms and 54 ms were found in the 80 mg, 120 mg, and 160 mg dose groups, respectively *[see Warnings and Precautions (5.1)]* No significant alteration in QRS interval was observed.

In a small study (n=25) of patients with implanted defibrillators treated concurrently with sotalol, 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 dose-response trial comparing three dose levels of sotalol, 80 mg, 120 mg, and 160 mg with placebo given q12h (or q24h in patients with a reduced renal creatinine clearance) for the prevention of recurrence of symptomatic atrial fibrillation (AFIB)/flutter (AFL), the mean ventricular rate during recurrence of AFIB/AFL was 125, 107, 110 and 99 beats/min in the placebo, 80 mg, 120 mg and 160 mg dose groups, respectively ($p<0.017$) for each sotalol dose group versus placebo). In another placebo controlled trial in which sotalol was titrated to a dose between 160 and 320 mg/day in patients with chronic AFIB, the mean ventricular rate during recurrence of AFIB was 107 and 84 beats/min in the placebo and sotalol groups, respectively ($p<0.001$).

Twenty-five children in an unblinded, multicenter trial with supraventricular (SVT) and/or ventricular (VT) tachyarrhythmias, aged between 3 days and 12 years (mostly neonates and infants), received an ascending titration regimen with daily doses of 30, 90 and 210 mg/m^2 with dosing every 8 hours for a total of 9 doses. During steady-state, the respective average increases above baseline of the QTc interval, in ms (%), were 2(+1%), 14(+4%) and 29(+7%) ms at the 3 dose levels. The respective mean maximum increases above baseline of the QTc interval, in ms (%), were 23(+6%), 36(+9%) and 55(+14%) ms at the 3 dose levels. The steady-state percent increases in the RR interval were 3, 9 and 12%. The smallest children (BSA <0.33m^2) showed a tendency for larger Class III effects (ΔQTc) and an increased frequency of prolongations of the QTc interval as compared with the larger children (BSA ≥0.33m^2). The beta-blocking effects also tended to be greater in the smaller children (BSA<0.33m^2). Both the Class II and beta-blocking effects of sotalol were linearly related with the plasma concentrations.

Hemodynamics: In a study of systemic hemodynamic function measured invasively in 12 patients with a mean LV ejection fraction of 37% and ventricular tachycardia (9 sustained and 3 non-sustained), a median dose of 160 mg twice daily of sotalol 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, and total peripheral resistance increases by a small amount.

In hypertensive patients, sotalol produces significant reductions in both systolic and diastolic blood pressures. Although sotalol is usually well-tolerated hemodynamically, in patients with marginal cardiac compensation, deterioration in cardiac performance may occur.

12.3 Pharmacokinetics

In healthy subjects, the oral bioavailability of sotalol 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 (i.e., after 5-6 doses when administered twice daily). Over the oral dosage range 160-640 mg/day sotalol 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 12 hours. Dosing every 12 hours results in trough plasma concentrations which are approximately one-half of those at peak.

Sotalol does not bind to plasma proteins and is not metabolized. Sotalol shows very little intersubject variability in plasma levels. The pharmacokinetics of the d and l enantiomers of sotalol are essentially identical. Sotalol crosses the blood brain barrier poorly. Excretion is predominantly via the kidney in the unchanged form, and therefore lower doses are necessary in conditions of renal impairment *[see Dosage and Administration (2)]*.

Age per se does not significantly alter the pharmacokinetics of sotalol, but impaired renal function in geriatric patients can increase the terminal elimination half-life, resulting in increased drug accumulation. The absorption of sotalol was reduced by approximately 20% compared to fasting when it was administered with a standard meal. Since sotalol is not subject to first-pass metabolism, patients with hepatic impairment show no alteration in clearance of sotalol.

The combined analysis of two unblinded, multicenter trials (a single dose and a multiple dose study) with 59 children, aged between 3 days and 12 years, showed the pharmacokinetics of sotalol to be first order. A daily dose of 30 mg/m^2 of sotalol was administered in the single dose study and daily doses of 30, 90 and 210 mg/m^2 were administered q8h in the multi-dose study. After rapid absorption with peak levels occurring on average between 2-3 hours following administration, sotalol was eliminated with a mean half-life of 9.5 hours. Steady-state was reached after 1-2 days. The average peak to trough concentration ratio was 2. BSA was the most important covariate and more relevant than age for the pharmacokinetics of sotalol. The smallest children (BSA <0.33 m^2) exhibited a greater drug exposure (+59%) than the larger children who showed a uniform drug concentration profile. The intersubject variation for oral clearance was 22%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed in rats during a 24-month study at 137-275 mg/kg/ day (approximately 3 times the maximum recommended human oral dose (MRHD) as mg/kg or 5 times the MRHD as mg/m^2) or in mice, during a 24-month study at 4141-7122 mg/kg/day (approximately 450-750 times the MRHD as mg/kg or 36-63 times the MRHD as mg/m^2). Sotalol has not been evaluated in any specific assay of mutagenicity or clastogenicity.

No significant reduction in fertility occurred in rats at oral doses of 1000 mg/kg/day (approximately 100 times the MRHD as mg/kg or 9 times the MRHD as mg/m^2) prior to mating, except for a small reduction in the number of offspring per litter.

Reproduction studies in rats and rabbits during organogenesis at 100 and 22 times the MRHD as mg/kg (9 and 7 times the MRHD as mg/m^2), respectively, did not reveal any teratogenic potential associated with sotalol HCl. In rabbits, a high dose of sotalol HCl (160 mg/kg/day) at 16 times the MRHD as mg/kg (6 times the MRHD as mg/m^2) produced a slight increase in fetal death likely due to maternal toxicity. Eight times the maximum dose (80 mg/kg/day or 3 times the MRHD as mg/m^2) did not result in an increased incidence of fetal deaths. In rats, 1000 mg/kg/day sotalol HCl, 100 times the MRHD (18 times the MRHD as mg/m^2), increased the number of early resorptions, while at 14 times the maximum dose (2.5 times the MRHD as mg/m^2), no increase in early resorptions was noted. However, animal reproduction studies are not always predictive of human response.

13.2 Animal Toxicology and/or Pharmacology

The LD_{50} of sotalol has been established in a variety of species. As the data in Table 5 show, LD_{50} is 100 to 1000 times more than the regular therapeutic dose:

Table 5: The LD_{50} of Sotalol in Different Species

Route of Administration	Species	LD_{50}
Oral	Rat	3450 mg/kg
Oral	Mouse	2600 mg/kg
Oral	Rabbit	1000 mg/kg
Intraperitoneal	Rat	680 mg/kg
Intraperitoneal	Mouse	670 mg/kg
Intraperitoneal	Dog	330 mg/kg
Intravenous	Mouse	166 mg/kg

14 CLINICAL STUDIES

There is no clinical experience with intravenous sotalol. However, because of the similarity of exposure of intravenous sotalol to oral sotalol, the expectation is that the efficacy will be similar.

14.1 Clinical Studies in Ventricular Arrhythmias

Sotalol has been studied in life-threatening and less severe arrhythmias. In patients with frequent premature ventricular complexes (VPC), orally administered sotalol was significantly superior to placebo in reducing VPCs, paired VPCs and non-sustained ventricular tachycardia (NSVT); the response was dose-related through 640 mg/day with 80-85% of patients having at least a 75% reduction of VPCs. Sotalol was also superior, at the doses evaluated, to propranolol (40-80 mg TID) and similar to quinidine (200-400 mg QID) in reducing VPCs. In patients with life-threatening arrhythmias [sustained ventricular tachycardia/fibrillation (VT/VF)], sotalol was studied acutely [by suppression of programmed electrical stimulation (PES) induced VT and by suppression of Holter monitor evidence of sustained VT] and, in acute responders, chronically.

In a double-blind, randomized comparison of oral sotalol and procainamide given intravenously (total of 2 mg/kg sotalol vs. 19 mg/kg of procainamide over 90 minutes), sotalol suppressed PES induction in 30% of patients vs. 20% for procainamide (p=0.2).

In a randomized clinical trial [Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) Trial] comparing choice of antiarrhythmic therapy by PES suppression vs. 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 was compared with 6 other drugs (procainamide, quinidine, mexiletine, propafenone, and imipramine). 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 vs. 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 yielded 41% response vs. 45% for the other drugs combined. Among responders placed on long term therapy identified acutely as effective (by either PES or Holter), Sotalol, when compared to the pool of other drugs, had the lowest two-year mortality (13% vs. 22%), the lowest two-year VT recurrence rate (30% vs. 60%), and the lowest withdrawal rate (38% vs. about 75-80%). The most commonly used doses of sotalol 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 vs. no pharmacologic treatment (e.g., in patients with implanted defibrillators) whether sotalol response causes improved survival or identifies a population with a good prognosis.

14.2 Clinical Studies in Supra-Ventricular Arrhythmias

Orally administered sotalol has been studied in patients with symptomatic AFIB/AFL in two principal studies, one in patients with primarily paroxysmal AFIB/AFL, the other in patients with primarily chronic AFIB.

In one study, a U.S., multicenter, randomized, placebo-controlled, double-blind, dose-response trial of patients with symptomatic primarily paroxysmal AFIB/AFL, three fixed dose levels of sotalol (80 mg, 120 mg and 160 mg) twice daily and placebo were compared in 253 patients. In patients with reduced creatinine clearance (40-60 mL/min) the same doses were given once daily. Patients were not randomized for the following reasons: QT >450 ms; creatinine clearance <40 mL/min; intolerance to beta-blockers; bradycardia-tachycardia syndrome in the absence of an implanted pacemaker; AFIB/AFL was asymptomatic or was associated with syncope, embolic CVA or TIA; acute myocardial infarction within the previous 2 months; congestive heart failure; bronchial asthma or other contraindications to beta-blocker therapy; receiving potassium losing diuretics without potassium replacement or without concurrent use of ACE-inhibitors; uncorrected hypokalemia (serum potassium <3.5 meq/L) or hypomagnesemia (serum magnesium <1.5 meq/L); received chronic oral amiodarone therapy for >1 month within previous 12 weeks; congenital or acquired long QT syndromes; history of Torsade de Pointes with other antiarrhythmic agents which increase the duration of ventricular repolarization; sinus rate <50 bpm during waking hours; unstable angina pectoris; receiving treatment with other drugs that prolong the QT interval; and AFIB/AFL associated with the Wolff-Parkinson-White (WPW) syndrome. If the QT interval increased to ≥520 ms (or JT >430 ms if QRS >100 ms) the drug was discontinued. The patient population in this trial was 64% male, and the mean age was 62 years. No structural heart disease was present in 43% of the patients. Doses were administered once daily in 20% of the patients because of reduced creatinine clearance.

Sotalol was shown to prolong the time to the first symptomatic, ECG-documented recurrence of AFIB/AFL, as well as to reduce the risk of such recurrence at both 6 and 12 months. The 120 mg dose was more effective than 80 mg, but 160 mg did not appear to have an added benefit. Note that these doses were given twice or once daily, depending on renal function. The results are shown in Figure 1 and Tables 6 and 7.

Figure 1
Study 1 – Time to First ECG-Documented Recurrence of Symptomatic AFIB/AFL Since Randomization

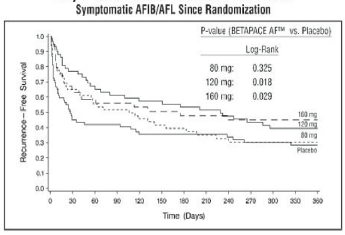


Table 6: Study 1 - Patient Status at 12 Months

	Placebo	Oral Sotalol Dose		
		80 mg	120 mg	160 mg
Randomized	69	59	63	62
On treatment in NSR at 12 months without recurrence[a]	23%	22%	29%	23%
Recurrence [a,b]	67%	58%	49%	42%
D/C for AEs	6%	12%	18%	29%

[a] Symptomatic AFIB/AFL

[b] Efficacy endpoint of Study 1; study treatment stopped.

Note that columns do not add up to 100% due to discontinuations (D/C) for "other" reasons.

Table 7: Study 1 - Median Time to Recurrence of Symptomatic AFIB/AFL and Relative Risk (vs. Placebo) at 12 Months

	Placebo	Oral Sotalol Dose		
		80 mg	120 mg	160 mg
p-value vs. placebo		p=0.325	p=0.018	p=0.029
Relative Risk (RR) to placebo		0.81	0.59	0.59
Median time to recurrence (days)	27	106	229	175

Discontinuation because of adverse events was dose related.

In a second multicenter, randomized, placebo-controlled, double-blind study of 6 months duration in 232 patients with chronic AFIB, sotalol was titrated over a dose range from 80 mg/day to 320 mg/day. The patient population of this trial was 70% male with a mean age of 65 years. Structural heart disease was present in 49% of the patients. All patients had chronic AFIB for >2 weeks but <1 year at entry with a mean duration of 4.1 months. Patients were excluded if they had significant electrolyte imbalance, QTc >460 ms, QRS >140 ms, any degree of AV block or functioning pacemaker, uncompensated cardiac failure, asthma, significant renal disease (estimated creatinine clearance <50 mL/min), heart rate <50 bpm, myocardial infarction or open heart surgery in past 2 months, unstable angina, infective endocarditis, active pericarditis or myocarditis, ≥3 DC cardioversions in the past, medications that prolonged QT interval, and previous amiodarone treatment. After successful cardioversion patients were randomized to receive placebo (n=114) or sotalol (n=118), at a starting dose of 80 mg twice daily. If the initial dose was not tolerated it was decreased to 80 mg once daily, but if it was tolerated it was increased to 160 mg twice daily. During the maintenance period 67% of treated patients received a dose of 160 mg twice daily, and the remainder received doses of 80 mg once daily (17%) and 80 mg twice daily (16%).

Figure 2 and Tables 8 and 9 show the results of the trial. There was a longer time to ECG-documented recurrence of AFIB and a reduced risk of recurrence at 6 months compared to placebo.

Table 8: Study 2 - Patient Status at 6 Months

Randomized	Oral Sotalol	Placebo
	118	114
On treatment in NSR at 6 months without recurrence[a]	45%	29%
Recurrence [a,b]	49%	67%
D/C for AEs	6%	3%
Death		1%

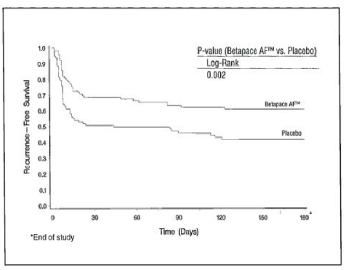
[a] Symptomatic or asymptomatic AFIB/AFL

[b] Efficacy endpoint of Study 2; study treatment stopped.

Table 9: Study 2 - Median Time to Recurrence of Symptomatic AFIB/AFL/Death and Relative Risk (vs. Placebo) at 6 Months

p-value vs. placebo	Oral Sotalol	Placebo
	p=0.002	
Relative Risk (RR) to placebo	0.55	
Median time to recurrence (days)	>180	44

Figure 2
Study 2 - Time to First ECG-Documented Recurrence of Symptomatic AFIB/AFL/Death Since Randomization



14.3 Clinical Studies in Patients with Myocardial Infarction

In a multicenter double-blind randomized study reported by Julian et al, the effect of sotalol 320 mg once daily was compared with that of placebo in 1456 patients (randomized 3:2, sotalol to placebo) surviving an acute myocardial infarction (MI). Treatment was started 5-14 days after infarction. Patients were followed for 12 months. The mortality rate was 7.3% in the sotalol group and 8.9% in the placebo group, not a statistically significant difference. Although the results do not show evidence of a benefit of sotalol in this population, they do not show an added risk in post MI patients receiving sotalol. There was, however, a suggestion of an early (i.e., first 10 days) excess mortality (3% on sotalol vs. 2% on placebo).

In a second small trial (n=17 randomized to sotalol) where sotalol was administered at high doses (e.g., 320 mg twice daily) to high-risk post-infarction patients (ejection fraction <40% and either >10 VPC/hr or VT on Holter), there were 4 fatalities and 3 serious hemodynamic/electrical adverse events within two weeks of initiating sotalol.

16 HOW SUPPLIED/STORAGE AND HANDLING

Intravenous sotalol is supplied in 10 mL vials, each containing 150 mg of sotalol hydrochloride (15 mg/mL).

NDC 69724-112-10
carton containing one, 10 mL vial

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from freezing and light.

Manufactured by:
Mylan Institutional
Galway, Ireland

Manufactured for:
ALTATHERA Pharmaceuticals LLC
Chicago, IL 60606 U.S.A.

17 PATIENT COUNSELING INFORMATION

Instruct patients to report syncopal events or new pre-syncopal symptoms, as these may be signs of either hypotension or Torsade de Pointes.

Instruct patients to inform a nurse or physician if pain or swelling develop at the infusion site, or if an alarm sounds from the infusion pump.