

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOTYLIZE™ safely and effectively. See full prescribing information for SOTYLIZE.

SOTYLIZE (sotalol hydrochloride) oral solution
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 interval between doses 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

SOTYLIZE is an antiarrhythmic indicated for:

- The treatment of life-threatening ventricular arrhythmias (1.1)
- The maintenance of normal sinus rhythm in patients with highly symptomatic atrial fibrillation/flutter (AFIB/AFL)(1.2)

DOSAGE AND ADMINISTRATION

- If creatinine clearance is between 60 and 40 mL/min, administer once daily, if less than 40 mL/min, sotalol is not recommended (2.1)
- Ventricular Arrhythmia: Initiate therapy at 80 mg. Increase the dose as needed in increments of 80 mg, every 3 days to a maximum 320 mg (2.2)
- Symptomatic AFIB/AFL: Initiate therapy at 80 mg. Increase the dose as needed in increments of 40 mg, every 3 days to a maximum 160 mg (2.3)
- Pediatrics: Dosage depends on age (2.2)

DOSAGE FORMS AND STRENGTHS

- 5 mg/mL oral solution (3)

CONTRAINDICATIONS

- Sinus bradycardia (<50 bpm), sick sinus syndrome or 2nd or 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)
- Hypersensitivity to sotalol (4)

WARNINGS AND PRECAUTIONS

- QT prolongation, bradycardia, AV block, hypotension, worsening heart failure: Reduce dose as needed (5.1, 5.3, 5.4, 5.5)
- Acute exacerbation of coronary artery disease upon cessation of therapy: Do not abruptly discontinue (5.8)
- Correct any electrolyte disturbances (5.9)
- May mask symptoms of hypoglycemia or worsen hyperglycemia in diabetic patients; monitor (5.12)

ADVERSE REACTIONS

Most common adverse reactions (>10%) seen with oral sotalol (dose related) are fatigue, bradycardia, dizziness, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Arbor Pharmaceuticals, LLC, at 1-866-516-4950 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 (7.4)
- Dose of beta-2 receptor agonists may have to be increased (7.5)
- Sotalol may potentiate rebound hypertension after discontinuation of clonidine (7.6)
- Aluminum or magnesium-based antacids reduce sotalol exposure (7.8)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Sotalol is secreted in human milk. Discontinue nursing or discontinue the drug (8.3)
- Pediatric Use: Safety and effectiveness have not been established, but beta-blocking and electrophysiological effects are seen in children (12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LIFE THREATENING PROARRHYTHMIA

1 INDICATIONS AND USAGE

- 1.1 Documented Life-Threatening Ventricular Arrhythmia
- 1.2 Delay in Recurrence of Atrial Fibrillation/Atrial Flutter

2 DOSAGE AND ADMINISTRATION

- 2.1 General Rules and Safety Measures of Oral Sotalol Therapy
- 2.2 Ventricular Arrhythmia
- 2.3 Symptomatic AFIB/AFL
- 2.4 Considerations in Renal Impairment

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 QT Prolongation and Proarrhythmia
- 5.2 Bradycardia/Heart Block
- 5.3 Sick Sinus Syndrome
- 5.4 Hypotension
- 5.5 Recent Acute MI
- 5.6 Abrupt Withdrawal
- 5.7 Electrolyte Disturbances
- 5.8 Renal Impairment
- 5.9 Non-Allergic Bronchospasm
- 5.10 Diabetes
- 5.11 Thyrotoxicosis
- 5.12 Anaphylaxis
- 5.13 Major Surgery

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Digoxin
- 7.2 Calcium-Blocking Drugs
- 7.3 Catecholamine-Depleting Agents
- 7.4 Insulin and Oral Antidiabetic Agents
- 7.5 Beta-2-Receptor Stimulants
- 7.6 Clonidine
- 7.7 Drugs that Prolong QT Interval and Antiarrhythmic Agents
- 7.8 Antacids

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Clinical Studies in Ventricular Arrhythmias
- 14.2 Clinical Studies in Supra-Ventricular Arrhythmias
- 14.3 Clinical Studies in Patients with Myocardial Infarction

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*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 oral sotalol, and patients who are converted from intravenous sotalol 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 interval between doses prolonged, or the drug discontinued.
- Adjust the dosing interval based on creatinine clearance.

1 INDICATIONS AND USAGE

1.1 Documented Life-Threatening Ventricular Arrhythmia

SOTYLIZE (sotalol hydrochloride) is indicated for the treatment of ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician are life-threatening.

Upon initiation of SOTYLIZE, increasing doses, and prior to chronic outpatient use, evaluated response by a suitable method (e.g., PES or Holter monitoring) at steady-state blood levels of drug.

Limitation of Use

SOTYLIZE may not enhance survival in patients with ventricular arrhythmias. Because of the proarrhythmic effects of SOTYLIZE [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.

1.2 Delay in Recurrence of Atrial Fibrillation/Atrial Flutter

SOTYLIZE 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.

Limitation of Use

Because sotalol can cause life-threatening ventricular arrhythmias, reserve it for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL that is easily reversed (by Valsalva maneuver, for example) should usually not be given SOTYLIZE.

2 DOSAGE AND ADMINISTRATION

2.1 General Rules and Safety Measures of Oral Sotalol Therapy

To minimize the risk of induced arrhythmia, patients initiated or re-initiated on sotalol should be hospitalized for at least 3 days or until steady-state drug levels are achieved, in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Initiate oral 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 sotalol. Measure serum creatinine and calculate an estimated creatinine clearance in order to establish the appropriate dosing interval for sotalol.

Start sotalol therapy only if the baseline QTc interval is <450 msec. During initiation and titration, monitor the QT interval after each dose. If the QTc interval prolongs to 500 msec or greater, reduce the dose, increase the interval between doses, or discontinue the drug.

Administer sotalol twice daily in patients with a creatinine clearance >60 mL/min or once daily in patients with creatinine clearance between 40 and 60 mL/min. Sotalol is not recommended in patients with a creatinine clearance <40 mL/min. The recommended initial oral dose of sotalol is 80 mg (once or twice daily) and is initiated and titrated as described below.

Patients to be discharged on SOTYLIZE therapy from an in-patient setting should have an adequate supply of SOTYLIZE, to allow uninterrupted therapy until the patient can fill a SOTYLIZE prescription.

Advise patients who miss a dose to take just the next dose at the usual time.

For patients discharged and taking compounded sotalol oral solution filled by the pharmacy, consider switching to SOTYLIZE while in an out-patient setting.

Table 1 shows the appropriate volume of SOTYLIZE solution for typical doses.

Table 1: SOTYLIZE Dose Volume

Dose	Volume of SOTYLIZE 5 mg/mL solution
80 mg	16 mL
120 mg	24 mL
160 mg	32 mL
240 mg	48 mL
320 mg	64 mL

2.2 Ventricular Arrhythmia

The recommended initial dose of oral sotalol for the treatment of ventricular arrhythmia is 80 mg, once or twice daily based on creatinine clearance [see *Dosage and Administration (2.1)*]. The dose may be increased in increments of 80 mg per day every 3 days as needed, provided QTc < 500 msec. The usual therapeutic effect is observed with oral doses of 80 to 160 mg once or twice a day. Oral doses as high as 240-320 mg once or twice a day have been utilized in patients with refractory life-threatening arrhythmias.

Pediatrics

As in adults, initiate in the hospital after appropriate clinical assessment, gradually increase dose as required, and monitor QT_c and heart rate.

For children aged 2 years and greater, with normal renal function, doses normalized for body surface area are appropriate for both initial and incremental dosing.

For initiation of treatment, 30 mg/m² three times a day (90 mg/m² total daily dose) is approximately equivalent to the initial 160 mg total daily dose for adults. Subsequent titration to a maximum of 60 mg/m² (approximately equivalent to the 360 mg total daily dose for adults) can then occur. Allow at least 36 hours between dose increments to attain steady-state plasma concentrations of sotalol in patients with normal renal function.

For children aged 2 years or younger, reduce the dose as shown in Figure 1.

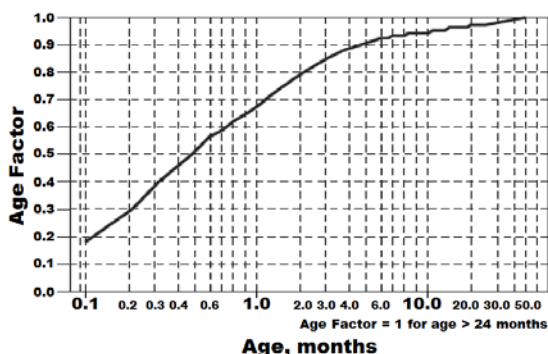


Figure 1. Factor for dose adjustment by age

For a child with normal renal function aged 1 month, the initial starting dose would be $(30 \times 0.7) = 21 \text{ mg/m}^2$, administered three times daily. For a child aged about 1 week, the initial starting dose should be multiplied by 0.3; the starting dose would be $(30 \times 0.3) = 9 \text{ mg/m}^2$. Use similar calculations for dose titration.

Since the half-life of sotalol increases below about 2 years, time to steady-state will also increase. Thus, in neonates the time to steady-state may be a week or longer.

2.3 Symptomatic AFIB/AFL

The recommended initial dose of oral sotalol for the treatment of symptomatic AFIB/AFL is 80 mg, once or twice daily based on creatinine clearance [see *Dosage and Administration (2.1)*]. If that dose level at steady-state does not acceptably reduce the time to

recurrence of arrhythmia and is tolerated with QTc <520 msec, increase the dose to 160 mg orally once or twice a day every three days. In the U.S. multicenter dose-response study, 120 mg orally once or twice a day was found to be the most effective dose in prolonging the time to ECG-documented symptomatic recurrence of AFIB/AFL.

2.4 Considerations in Renal Impairment

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 and it will take much longer to reach steady-state with any dose and/or frequency of administration.

3 DOSAGE FORMS AND STRENGTHS

Oral solution: 5 mg/mL, in 250 mL or 480 mL bottles.

4 CONTRAINDICATIONS

- Sinus bradycardia (<50 bpm during waking hours), sick sinus syndrome or second and third degree AV block unless a functioning pacemaker is present
- Congenital or acquired long QT syndromes, baseline 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

Ventricular arrhythmias

SOTYLIZE 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 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 the QT interval. [see *Dosage and Administration (2)*].

Use with Drugs that Prolong QT Interval and Antiarrhythmic Agents

The use of SOTYLIZE 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, certain oral macrolides and certain quinolone antibiotics. 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 sotalol because of their potential to prolong refractoriness. There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics.

5.2 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% of patients. Bradycardia itself increases the risk of Torsade de Pointes, so carefully monitor patients receiving concomitant digoxin.

5.3 Sick Sinus Syndrome

In general, SOTYLIZE 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 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.

5.4 Hypotension

Sotalol produces significant reductions in both systolic and diastolic blood pressures and may result in hypotension, including decompensated heart failure. Monitor hemodynamics in patients with marginal cardiac compensation.

5.5 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.

5.6 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 alternate 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.

5.7 Electrolyte Disturbances

SOTYLIZE 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.

5.8 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)*].

5.9 Non-Allergic Bronchospasm

Patients with bronchospastic diseases should in general not receive beta-blockers. If SOTYLIZE is to be administered, use the smallest effective dose, to minimize inhibition of bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta₂ receptors.

5.10 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.

5.11 Thyrotoxicosis

Beta-blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Avoid abrupt withdrawal of SOTYLIZE which might exacerbate symptoms of hyperthyroidism, including thyroid storm.

5.12 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.

5.13 Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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.

Adults:

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.

Serious Adverse Reactions

SOTYLIZE 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 *Warnings 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 msec in the 80, 120, and 160 mg groups, respectively, in the oral dose-response study [see *Clinical Trials (14.2)*].

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 2 below.

Table 2: 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

Table 3 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.

Table 3: Relationship Between QT_c Interval Prolongation and Torsade de Pointes

On-Therapy QT _c Interval (msec)	Incidence of Torsade de Pointes	Change in QT _c Interval From Baseline (msec)	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 QT_c 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.

Other Adverse Reactions

In a pooled clinical trial population consisting of four placebo-controlled studies with 275 patients with AFIB/AFL treated with 160-320 mg of oral sotalol, the following adverse events were reported at least 2% more frequently in the 160-240 mg sotalol treated

patients than in placebo patients (see Table 4). The data are presented by incidence of events in the oral sotalol and placebo groups by body system and daily dose.

Table 4: Incidence (%) of Common Adverse Reactions (≥2% more frequent in patients treated in the 160-240 mg group than on placebo) in Four Placebo-Controlled Studies of Patients with AFIB/AFL Treated with Oral Sotalol

Body System/ Adverse Reactions (Preferred Term)	Placebo N=282	Oral Sotalol Total Daily Dose	
		160- 240 N=153	>240-320 N=122
CARDIOVASCULAR			
Bradycardia	2.5	13.1	12.3
Abnormality ECG	0.4	3.3	2.5
GASTROINTESTINAL			
Nausea/Vomiting	5.3	7.8	5.7
Diarrhea	2.1	5.2	5.7
GENERAL			
Fatigue	8.5	19.6	18.9
Hyperhidrosis	3.2	5.2	4.9
Weakness	3.2	5.2	4.9
NERVOUS SYSTEM			
Dizziness	12.4	16.3	13.1

In AFIB/AFL patients, discontinuation because of unacceptable adverse reactions was necessary in 17% of the patients, and occurred in 10% of patients less than two weeks after starting treatment. The most common adverse reactions 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 were similar to those described for the AFIB/AFL population.

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.

Pediatric Patients:

In an unblinded multicenter trial of 25 patients with SVT and/or VT receiving daily doses of 30, 90 and 210 mg/m² 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/m² daily, was discontinued because of increased frequency of sinus pauses/bradycardia. Additional cardiovascular adverse events were seen at the 90 and 210 mg/m² 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 QT_c ≥525 msec were seen in 2 patients at the 210 mg/m² 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 estimate reliably their frequency or establish a causal relationship to drug exposure.

Postmarketing experience with sotalol shows an adverse event 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, alopecia.

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, certain oral macrolides and certain quinolone antibiotics. 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 sotalol because of their potential to prolong refractoriness [*see Warnings and Precautions (5.2)*]. There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics.

7.8 Antacids

Administration of oral sotalol within 2 hours of antacids containing aluminum oxide and magnesium hydroxide should be avoided because it may result in a reduction in C_{max} and AUC of 26% and 20%, respectively, and consequently in a 25% reduction in the bradycardic effect at rest. Administration of the antacid two hours after oral sotalol has no effect on the pharmacokinetics or pharmacodynamics of sotalol.

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). Animal reproduction studies are not always predictive of human response.

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 of 2.5 times the MRHD produced no increase in early resorptions.

8.3 Nursing Mothers

Sotalol is excreted in the milk of laboratory animals and has been reported to be present in human milk. Discontinue nursing or SOTYLIZE.

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 (QT_c interval and resting heart rate) and drug concentrations have been evaluated in children aged between 3 days and 12 years old [*see Dosage and Administration (2.2) and Clinical Pharmacology (12)*].

8.5 Geriatric Use

Impaired renal function in geriatric patients can increase the terminal elimination half-life, resulting in increased drug accumulation [*see Clinical Pharmacology (12.3)*].

8.6 Patients with 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)*]. The dosing interval (time between divided doses) of sotalol should be modified when creatinine clearance is lower than 60 mL/min [see *Dosage and Administration (2.4)*]. Sotalol is contraindicated when creatinine clearance is less than 40 mL/min [see *Contraindications (4)*].

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.

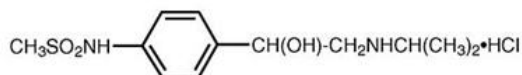
Bronchospasm: Aminophylline or aerosol beta-2-receptor stimulant.

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

SOTYLIZE is an aqueous solution containing sotalol hydrochloride.

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-1-N-[4-[1-hydroxy-2-[(1-methylethyl) amino]ethyl]phenyl]methane-sulfonamide monohydrochloride. The molecular formula is C₁₂H₂₀N₂O₃S HCl and is represented by the following structural formula:



SOTYLIZE is a grape flavored aqueous solution. Each mL contains 5 mg sotalol HCl. Inactive ingredients are sodium citrate, citric acid, sucralose, sodium benzoate and purified water.

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. Sotalol hydrochloride is a racemic mixture of two isomers, both of which 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 an oral dose of about 80 mg/day and maximal at 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/m² 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/m² 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 III 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 msec in QT and 10-40 msec in QT_c. 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 msec, 40 msec and 54 msec 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 every 12 hours (or every 24 hours 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/m² with dosing every 8 hours for a total of 9 doses. During steady-state, the respective average increases above baseline of the QT_c interval, in msec (%), were 2(+1%), 14(+4%) and 29(+7%) msec at the 3 dose levels. The respective mean maximum increases above baseline of the QT_c interval, in msec (%), were 23(+6%), 36(+9%) and 55(+14%) msec at the 3 dose levels. The steady-state percent increases in the RR interval were 3, 9 and 12%. The smallest children (BSA<0.33m²) showed a tendency for larger Class III effects (ΔQT_c) and an increased frequency of prolongations of the QT_c interval as compared with the larger children (BSA≥0.33m²). The beta-blocking effects also tended to be greater in the smaller children (BSA<0.33m²). Both the Class III 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 [see *Warnings and Precautions (5.5)*].

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 (2.1)*]. 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/m² of sotalol was administered in the single dose study and daily doses of 30, 90 and 210 mg/m² were administered every 8 hours 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 <0.33m²) 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 30 times the maximum recommended human oral dose (MRHD) as mg/kg or 5 times the MRHD as mg/m²) 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/m²).

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/m²) 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/m²), 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/m²) 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/m²) 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/m²), increased the number of early resorptions, while at 14 times the maximum dose (2.5 times the MRHD as mg/m²), no increase in early resorptions was noted. However, animal reproduction studies are not always predictive of human response.

14 CLINICAL STUDIES

14.1 Clinical Studies in Ventricular Arrhythmias

Oral sotalol has been studied in life-threatening and less severe arrhythmias. In patients with frequent premature ventricular complexes (VPC), 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 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 hydrochloride 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 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 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

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 hydrochloride (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 msec; 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 msec (or JT ≥ 430 msec if QRS >100 msec) 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 2, Table 5 and Table 6.

Figure 2: Study 1 – Time to First ECG-Documented Recurrence of Symptomatic AFIB/AFL Since Randomization

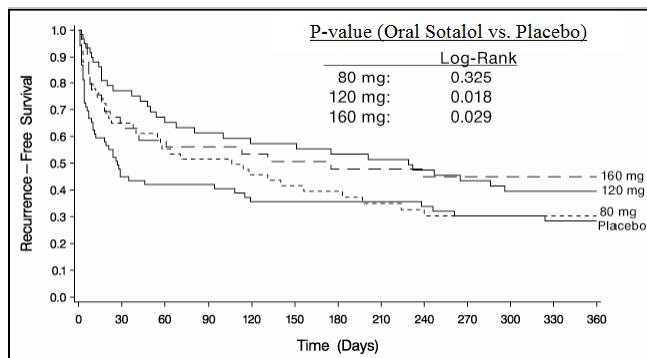


Table 5: Study 1 – Patient Status at 12 Months

	Placebo	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 ^{ab}	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 6: 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, oral 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 msec, QRS >140 msec, 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%).

Tables 7 and 8 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.

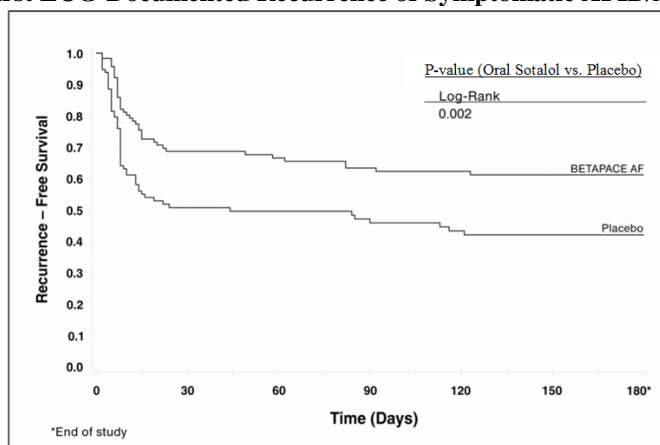
Table 7: Study 2 – Patient Status at 6 Months

Randomized	Oral Sotalol	Placebo
	118	114
On treatment in NSR at 6 months without recurrence ^a	45%	29%
Recurrence ^{ab}	49%	67%
D/C for AEs	6%	3%
Death		1%
^a Symptomatic or asymptomatic AFIB/AFL		
^b Efficacy endpoint of Study 2; study treatment		

Table 8: 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 3: 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, 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 postinfarction 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

SOTYLIZE (sotalol hydrochloride) is supplied as follows:

- NDC 24338-530-25, 5 mg/mL: 250 mL bottle
- NDC 24338-530-48, 5 mg/mL: 480 mL bottle

16.1 Storage

Store at 20°C to 25°C (68°F -77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Information.

QT Prolongation and Proarrhythmia

Advise patients to contact their healthcare provider in the event of syncope, pre-syncope symptoms and cardiac palpitations such as fainting, dizziness or fast heartbeats. Advise patients that their healthcare provider will monitor their electrolytes and ECG during treatment [see *Warnings and Precautions* (5.1)].

Diarrhea, Unusual Sweating, Vomiting, Reduced Appetite, Excessive Thirst

Advise patients to contact their healthcare provider in the event of conditions conducive to electrolyte changes such as severe diarrhea, unusual sweating, vomiting, less appetite than normal or excessive thirst [see *Warnings and Precautions* (5.9)].

Administration

Advise patients to not change the SOTYLIZE dose prescribed by their healthcare provider.

Advise patients that, to be sure doses are accurately measured, doses for children and infants should be measured using an appropriate measuring device such as an oral syringe. Advise them that a teaspoon or tablespoon should not be used to measure SOTYLIZE doses since doing so might lead to confusion and the wrong dose.

Advise patients that they should not miss a dose, but if they do miss a dose they should not double the next dose to compensate for the missed dose; they should take the next dose at the regularly scheduled time [see *Dosage and Administration (2)*].

Advise patients to not interrupt or discontinue SOTYLIZE without their physician's advice, that they should get their prescription for sotalol filled and refilled on time so they do not interrupt treatment [see *Dosage and Administration (2.1)*].

Advise patients that they should not take SOTYLIZE if they also take another medicine that contains sotalol.

Advise patients that if overdose occurs or they take too much SOTYLIZE, take their SOTYLIZE medicine bottle with them and go to the nearest emergency room immediately. Overdoses can potentially cause life-threatening abnormal heart beats and possibly death.

Advise patients to contact their healthcare provider if they develop bradycardia.

Drug Interactions

Advise patients not to start taking other medications without first discussing new medications with their healthcare provider.

Antacids

Advise patients that they should avoid taking SOTYLIZE within 2 hours of taking antacids that contain aluminum oxide or magnesium hydroxide [see *Drug Interactions (7.8)*].

Rx Only

Manufactured for:



Atlanta, GA 30328

Manufactured by:

Patheon Inc.

Whitby Region Operations

111 Consumers Drive

Whitby, ON L1N 5Z5 Canada

Distributed By Arbor Pharmaceuticals, LLC, Atlanta, GA 30328

SOTYLIZE is a trademark of Arbor Pharmaceuticals, LLC

© 2014 Arbor Pharmaceuticals, LLC

PATIENT INFORMATION

SOTYLIZE (so-tih-lize) (sotalol hydrochloride) oral solution

Read this Patient Information before you start taking SOTYLIZE and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about SOTYLIZE?

SOTYLIZE contains sotalol. Sotalol can cause serious side effects, including a type of abnormal heartbeat called Torsade de Pointes, that can lead to death.

Treatment with SOTYLIZE must be started or re-started in a hospital. You must have continuous monitoring of the electrical activity of your heart by electrocardiogram (ECG) and tests of your kidney function for at least the first 3 days of treatment. This will allow your doctor to determine the right dose of SOTYLIZE for you. It is important that when you go home, you take the exact dose of SOTYLIZE that your doctor prescribes for you.

Your doctor will continue to do ECGs to monitor your heart and check your kidney function, and also check the levels of body salts (electrolyte) in your blood, as needed during treatment with SOTYLIZE.

Call your doctor right away if you have any of the following symptoms that may be signs of an irregular heartbeat:

- fainting
- dizziness
- fast heartbeat

What is SOTYLIZE?

SOTYLIZE is a prescription medicine used:

- to treat life-threatening heart rhythm problems called ventricular arrhythmias.
Medicines used to treat life-threatening heartbeat problems may not help you live longer.
- to increase the amount of time between having symptoms of heart rhythm disorders called atrial fibrillation or atrial flutter

Who should not take SOTYLIZE?

Do not take SOTYLIZE if you:

- have a very slow heartbeat or certain heart conditions called sick sinus syndrome or heart block, and you do not have an implanted pacemaker
- have a heart problem called congenital long QT syndrome, or develop long QT syndrome
- have uncontrolled heart failure
- have certain kidney problems
- have been told by your doctor that you have a low level of potassium in your blood
- have asthma or other lung or breathing problems that cause shortness of breath or wheezing
- are allergic to sotalol

What should I tell my doctor before taking SOTYLIZE?

Before you take SOTYLIZE, tell your doctor if you:

- have had a severe allergic reaction to anything in the past. See **“What are the possible side effects of SOTYLIZE?”**
- have heart problems
- have kidney problems
- have asthma, or other lung or breathing problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if SOTYLIZE will harm your unborn baby. Talk to your doctor about if SOTYLIZE is right for you during pregnancy.
- are breastfeeding or plan to breastfeed. SOTYLIZE can pass into your milk and may harm your baby. You and your doctor should decide if you will take SOTYLIZE or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking SOTYLIZE with other medicines can cause serious side effects. Tell your doctor if you take another medicine that contains sotalol. You should not take SOTYLIZE if you also take another medicine that contains sotalol. You should not take SOTYLIZE if you also take another medicine that contains sotalol.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take SOTYLIZE?

- Take SOTYLIZE exactly as your doctor tells you to take it.
- Do not stop taking or change your dose of SOTYLIZE unless your doctor tells you to. If you stop taking SOTYLIZE suddenly, your heart problems may become worse.
- When it is time to stop taking SOTYLIZE, your doctor will give you instructions on how to slowly reduce your dose over a period of 1 to 2 weeks.
- Do not run out of your supply of SOTYLIZE. When you are discharged from the hospital after starting treatment with SOTYLIZE, it is important for you to have enough SOTYLIZE to take until you are able to fill your prescription for SOTYLIZE.
- If you miss a dose of SOTYLIZE, take your next dose at the usual time. Do not take 2 doses at the same time.
- It is important to accurately measure each SOTYLIZE dose. To measure the correct amount of SOTYLIZE to give, use an appropriate measuring device such as an oral syringe for children and infants. You can get oral syringes at your pharmacy. Do not use a teaspoon or tablespoon to measure SOTYLIZE doses since this may lead to confusion and the wrong dose.
- If you take an antacid medicine that contains aluminum oxide or magnesium hydroxide during treatment with SOTYLIZE, take the antacid at least 2 hours before or at least 2 hours after you take SOTYLIZE.
- If you overdose or take too much SOTYLIZE, take your SOTYLIZE medicine bottle with you and go to the nearest emergency room right away. Overdoses can potentially cause life-threatening abnormal heart beats and possibly death.

What are the possible side effects of SOTYLIZE?

SOTYLIZE can cause serious side effects, including:

- See **“What is the most important information I should know about SOTYLIZE?”**
- **Slow heartbeat (bradycardia)** is common with SOTYLIZE. A slow heartbeat increases your risk of developing a serious abnormal heartbeat. See **“What is the most important information I should know about SOTYLIZE?”** Your doctor will check you for this problem, especially if you take the medicine digoxin.

- **New or worsening heart failure** can happen in people who take SOTYLIZE. Symptoms of worsening heart failure include shortness of breath and fatigue. If these occur, contact your doctor.
- **If you have diabetes**, SOTYLIZE can make it more difficult for you to tell if you have low blood sugar (hypoglycemia). Certain important signs of low blood sugar, such as a fast heartbeat, may be hidden.
- **If you have an overactive thyroid gland (hyperthyroidism)**, SOTYLIZE can make it more difficult for you to tell if you are having symptoms of too much thyroid hormone in your blood. Certain signs of having too much thyroid hormone in your blood, such as a fast heartbeat, may be hidden. If you stop taking SOTYLIZE suddenly, your symptoms of having too much thyroid hormone in your blood may become much worse, and could be life-threatening.
- **Severe allergic reactions.** People who have had severe allergic reactions in the past to other things may have a more severe allergic reaction when taking medicines like SOTYLIZE.
- **Possible side effects to anesthesia.** SOTYLIZE may cause severe low blood pressure and heart rhythm problems in people who receive anesthesia for major surgery. Tell your doctor that you are taking SOTYLIZE if you need to have surgery during treatment with SOTYLIZE.

The most common side effects of SOTYLIZE include:

- tiredness
- slow heart rate
- dizziness
- headache

Changes in the level of body salts (electrolytes) in your blood can lead to serious side effects during treatment with SOTYLIZE. Call your doctor if you have any of the following symptoms:

- severe diarrhea
- unusual sweating
- vomiting
- less appetite than normal
- increased thirst (drinking more than normal)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of SOTYLIZE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SOTYLIZE?

- Store SOTYLIZE at room temperature between 68°F to 77°F (20°C to 25°C).

Keep SOTYLIZE and all medicines out of the reach of children.

General information about the safe and effective use of SOTYLIZE

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SOTYLIZE for a condition for which it was not prescribed. Do not give SOTYLIZE to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about SOTYLIZE that is written for health professionals.

For more information, go to www.SOTYLIZE.com or call 1-866-516-4950.

What are the ingredients in SOTYLIZE?

Active ingredient: sotalol hydrochloride

Inactive ingredients: sodium citrate, citric acid, sucralose, sodium benzoate, and purified water

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:



Atlanta, GA 30328

Manufactured by:

Patheon Inc.

Whitby Region Operations

111 Consumers Drive

Whitby, ON L1N 5Z5 Canada

Distributed by: Arbor Pharmaceuticals, LLC, Atlanta, GA 30328

Issued: Month/Year

SOTYLIZE is a trademark of Arbor Pharmaceuticals, LLC

© 2014 Arbor Pharmaceuticals, LLC