SOTALAR Tablets (Sotalol)

Composition

SOTALAR 40
Each tablet contains:
Sotalol hydrochloride........ 40 mg

Dosage Forms

Tablet

Pharmacology

Pharmacodynamics

D,L-sotalol is a non-selective hydrophilic beta-adrenergic receptor blocking agent, devoid of intrinsic sympathomimetic activity or membrane stabilizing activity. Sotalol has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties. Sotalol has no known effect on the upstroke velocity and therefore no effect on the depolarisation phase.

Sotalol uniformly prolongs the action potential duration in cardiac tissues by delaying the repolarisation phase. Its major effects are prolongation of the atrial, ventricular and accessory pathway effective refractory periods. The Class II and III properties may be reflected on the surface electrocardiogram by a lengthening of the PR, QT and QTc (QT corrected for heart rate) intervals with no significant alteration in the QRS duration.

The d- and l-isomers of sotalol have similar Class III antiarrhythmic effects while the l-isomer is responsible for virtually all of the beta-blocking activity. Although significant beta-blockade may occur at oral doses as low as 25 mg, Class III effects are usually seen at daily doses of greater than 160 mg.

Its beta-adrenergic blocking activity causes a reduction in heart rate (negative chronotropic effect) and a limited reduction in the force of contraction (negative inotropic effect). These cardiac changes reduce myocardial oxygen consumption and cardiac work. Like other beta-blockers, sotalol inhibits renin release. The renin-suppressive effect of sotalol is significant both at rest and during exercise. Like other beta-adrenergic blocking agents, sotalol produces a gradual but significant reduction in both systolic and diastolic blood pressures in hypertensive patients. Twenty-four-hour control of blood pressure is maintained both in the supine and upright positions with a single daily dose.

Pharmacokinetics

Absorption
The bioavailability of oral sotalol is essentially complete (greater than 90%). After oral administration, peak levels are reached in 2.5 to 4 hours, and steady-state plasma levels are attained within 2-3 days. The absorption is reduced by approximately 20% when administered with a standard meal, in comparison to fasting conditions. Over the dosage range
40-640 mg/day, sotalol displays dose proportionality with respect to plasma levels.

Distribution
Distribution occurs to a central (plasma) and a peripheral compartment. Sotalol does not bind to plasma proteins. There is very little inter-subject variability in plasma levels. Sotalol crosses the blood brain barrier poorly, with cerebrospinal fluid concentrations only 10% of those in plasma.

Metabolism
Sotalol does not bind to plasma proteins and is not metabolized.

Excretion
The primary route of elimination is renal excretion. Approximately 80 to 90% of a dose is excreted unchanged in the urine, while the remainder is excreted in the feces.

Special Populations
Geriatric: Age does not significantly alter the pharmacokinetics, although impaired renal function in geriatric patients can decrease the excretion rate, resulting in increased drug accumulation.
Renal Impairment: Impaired renal function can decrease the excretion rate, resulting in increased drug accumulation. Lower doses are necessary in conditions of renal impairment.

Indications
- Ventricular Arrhythmias
  - Treatment of life-threatening ventricular tachyarrhythmias (VT);
  - Treatment of symptomatic non-sustained VT.
- Supraventricular Arrhythmias
  - Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation (AF), paroxysmal atioventricular (AV) nodal re-entrant tachycardia, paroxysmal AV re-entrant tachycardia using accessory pathways, and paroxysmal supraventricular tachycardia after cardiac surgery;
  - Maintenance of normal sinus rhythm following conversion of AF or atrial flutter.

Dosage And Administration
The initiation of treatment or changes in dosage with SOTALAR should follow an appropriate medical evaluation including electrocardiogram (ECG) control with measurement of the corrected QT interval, and assessment of renal function, electrolyte balance, and concomitant medications.

As with other antiarrhythmic agents, it is recommended that SOTALAR be initiated and doses increased in a facility capable of monitoring and assessing cardiac rhythm. The dosage must be individualized and based on the patient's response. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dosage adjustment.

In view of its beta-adrenergic blocking properties, treatment with SOTALAR should not be discontinued suddenly, especially in patients with ischemic heart disease or hypertension, to prevent exacerbation of the disease.

The following dosing schedule can be recommended:
The initial dose is 80 mg, administered either singly or as two divided doses. Oral dosage of SOTALAR should be adjusted gradually allowing 2-3 days between dosing increments in order to attain steady-state, and to allow monitoring of QT intervals. Most patients respond to a daily dose of 160 to 320 mg administered in two divided doses at approximately 12 hour intervals. Some patients with life-threatening refractory ventricular arrhythmias may require doses as high as 480 - 640 mg/day. These doses should be used under specialist supervision and should only be prescribed when the potential benefit outweighs the increased risk of adverse events, particularly proarrhythmias.
Renal Impairment

Because sotalol is excreted mainly in urine, the dosage of sotalol should be reduced when the creatinine clearance is less than 60 ml/min according to the following table:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Adjusted dose of SOTALAR tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Recommended Dose</td>
</tr>
<tr>
<td>30-60</td>
<td>1/2 recommended Dose</td>
</tr>
<tr>
<td>10-30</td>
<td>1/4 recommended Dose</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Avoid SOTALAR</td>
</tr>
</tbody>
</table>

The creatinine clearance can be estimated from serum creatinine by the Cockroft and Gault formula:

\[
\text{Men: } \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}
\]

\[
\text{Women: } \text{idem x 0.85}
\]

When serum creatinine is given in micro-mol/l, divide the value by 88.4 (1mg/dl = 88.4 micro-mol/l).

Hepatic Impairment

No dosage adjustment is required in hepatically impaired patients.

Pediatric Use

Sotalol is not intended for administration to children.

Contraindications

- Sick sinus syndrome
- Second- and third-degree AV heart block unless a functioning pacemaker is present
- Congenital or acquired long QT syndromes
- Torsades de pointes (TdP)
- Symptomatic sinus bradycardia
- Uncontrolled congestive heart failure
- Cardiogenic shock
- Anesthesia that produces myocardial depression
- Untreated pheochromocytoma
- Hypotension (except due to arrhythmia)
- Raynaud's phenomenon and severe peripheral circulatory disturbances
Warnings And Precautions

Drug Interactions

Antiarrhythmics
Class Ia antiarrhythmic drugs, such as disopyramide, quinidine and procainamide and other antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with sotalol, because of their potential to prolong refractoriness. The concomitant use of other beta-blocking agents with SOTALAR may result in additive Class II effects.

Other Drugs Prolonging the QT-interval
Sotalol should be given with extreme caution in conjunction with other drugs known to prolong the QT-interval such as phenothiazines, tricyclic antidepressants, terfenadine and astemizole. Other drugs that have been associated with an increased risk for TdP include erythromycin IV, halofantrine, pentamidine, and quinolone antibiotics.

Floctafenine
Beta-adrenergic blocking agents may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Calcium Channel Blocking Drugs
Concurrent administration of beta-blocking agents and calcium channel blockers has resulted in hypotension, bradycardia, conduction defects, and cardiac failure. Beta-blockers should be avoided in combination with cardiodepressant calcium-channel blockers such as verapamil and diltiazem because of the additive effects on AV conduction, and ventricular function.

Potassium-Depleting Diuretics
Hypokalemia or hypomagnesemia may occur, increasing the potential for TdP.

Other Potassium-Depleting Drugs
Amphotericin B, corticosteroids (systemic administration) and some laxatives may also be associated with hypokalemia; potassium levels should be monitored and corrected appropriately during concomitant administration with sotalol.

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

Digitalis Glycosides
Single and multiple doses of sotalol do not significantly affect serum digoxin levels. Proarrhythmic events were more common in sotalol-treated patients also receiving digitalis glycosides; however, this may be related to the presence of congestive heart failure (CHF), a known risk factor for proarrhythmia, in patients receiving digitalis glycosides. Association of digitalis glycosides with beta-blockers may increase auriculo-ventricular conduction time.

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

Insulin and Oral Hypoglycemics
Hyperglycemia may occur, and the dosage of antidiabetic drugs may require adjustment. Symptoms of hypoglycemia
(tachycardia) may be masked by beta-blocking agents.

Neuromuscular Blocking Agents (e.g. Tubocurarin)
The neuromuscular blockade is prolonged by beta-blocking agents.

Beta₂-receptor Stimulants
Patients in need of beta-agonists should not normally receive sotalol. However, if concomitant therapy is necessary, beta-agonists may have to be administered in increased dosages.

Proarrhythmias

The most dangerous adverse effect of Class I and Class III antiarrhythmic drugs (such as sotalol) is the aggravation of pre-existing arrhythmias or the provocation of new arrhythmias. Drugs that prolong the QT-interval may cause TdP, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. Experience to date indicates that the risk of TdP is associated with the prolongation of the QT-interval, reduction of the heart rate, reduction in serum potassium and magnesium, high plasma sotalol concentrations and with the concomitant use of sotalol and other medications which have been associated with TdP. Females may be at increased risk of developing TdP. The incidence of TdP is dose dependent. TdP usually occurs within 7 days of initiating therapy or escalation of the dose and can progress to ventricular fibrillation (VF).

In clinical trials of patients with sustained VT/VF the incidence of severe proarrhythmia (TdP or new sustained VT/VF) was <2% at doses up to 320 mg. The incidence more than doubled at higher doses.

Other risk factors for TdP were excessive prolongation of the QTC and history of cardiomegaly or congestive heart failure. Patients with sustained ventricular tachycardia and a history of congestive heart failure have the highest risk of serious proarrhythmia (7%).

Proarrhythmic events must be anticipated not only on initiating therapy but with every upward dose adjustment. Initiating therapy at 80 mg with gradual upward dose titration thereafter reduces the risk of proarrhythmia. In patients already receiving sotalol, caution should be used if the QTC exceeds 500 msec whilst on therapy, and serious consideration should be given to reducing the dose or discontinuing therapy when the QTC-interval exceeds 550 msec. Due to the multiple risk factors associated with TdP, however, caution should be exercised regardless of the QTC-interval.

Electrocardiographic Changes

Excessive prolongation of the QT-interval, >500 msec, can be a sign of toxicity and should be avoided. Sinus bradycardia has been observed very commonly in arrhythmia patients receiving sotalol in clinical trials. Bradycardia increases the risk of TdP. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of second- or third-degree AV block is approximately 1%

Abrupt Withdrawal

Hypersensitivity to catecholamines is observed in patients withdrawn from beta-blocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias, and in some cases, MI have been reported after abrupt discontinuation of therapy. Patients should be carefully monitored when discontinuing chronically administered SOTALAR, particularly those with ischemic heart disease. If possible the dosage should be gradually reduced over a period of one to two weeks, if necessary at the same time initiating replacement therapy. Abrupt discontinuation may unmask latent coronary insufficiency. In addition, hypertension may develop.

Electrolyte Disturbances

Sotalol should not be used in patients with hypokalaemia or hypomagnesemia prior to correction of imbalance; these conditions can exaggerate the degree of QT prolongation, and increase the potential for TdP. Special attention should be
given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or patients receiving concomitant magnesium- and/or potassium-depleting drugs.

### Congestive Heart Failure

Beta-blockade may further depress myocardial contractility and precipitate more severe heart failure. Caution is advised when initiating therapy in patients with left ventricular dysfunction controlled by therapy (i.e. angiotensin converting enzyme (ACE) inhibitors, diuretics, digitalis, etc); a low initial dose and careful dose titration is appropriate.

### Recent MI

In post-infarction patients with impaired left ventricular function, the risk versus benefit of sotalol administration must be considered. Careful monitoring and dose titration are critical during initiation and follow-up of therapy. SOTALAR should be avoided in patients with left ventricular ejection fractions

### Anaphylaxis

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

### Anesthesia

As with other beta-blocking agents, sotalol should be used with caution in patients undergoing surgery and in association with anesthetics that cause myocardial depression, such as cyclopropane or trichloroethylene.

### Diabetes Mellitus

Sotalol should be used with caution in patients with diabetes (especially labile diabetes) or with a history of episodes of spontaneous hypoglycemia, since beta-blockade may mask some important signs of the onset of acute hypoglycemia, e.g. tachycardia.

### Thyrotoxicosis

Beta-blockade may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade which might be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm.

### Psoriasis

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

### Drug/Laboratory Interaction

The presence of sotalol in the urine may result in falsely elevated levels of urinary metanephrine when measured by photometric methods. Patients suspected of having pheochromocytoma and who are treated with sotalol should have their urine screened utilizing the HPLC assay with solid phase extraction.

### Renal Impairment

As sotalol is mainly eliminated via the kidneys the dose should be adjusted in patients with renal impairment.

### Hepatic Impairment

No dosage adjustment is required in patients with hepatic impairment.

### Pregnancy
Animal studies with sotalol have shown no evidence of teratogenicity or other harmful effects on the fetus. Although there are no adequate and well-controlled studies in pregnant women, sotalol has been shown to cross the placenta and is found in amniotic fluid. Beta-blockers reduce placental perfusion, which may result in intrauterine fetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycemia and bradycardia) may occur in fetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Therefore, SOTALAR should be used in pregnancy only if the potential benefits outweigh the possible risk to the fetus. The neonate should be monitored very carefully for 48 - 72 hours after delivery if it was not possible to interrupt maternal therapy with SOTALAR 2-3 days before the birthdate.

▶ Lactation

Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is therefore not recommended during administration of SOTALAR.

▶ Pediatric Use

SOTALAR is not intended for administration in children.

▶ Geriatric Use

Age does not significantly alter the pharmacokinetics, although impaired renal function in geriatric patients can decrease the excretion rate, resulting in increased drug accumulation.

Undesirable Effects

The most frequent adverse effects of sotalol arise from its beta-blockade properties. Adverse effects are usually transient in nature and rarely necessitate interruption of, or withdrawal from treatment. If they do occur, they usually disappear when the dosage is reduced. The most significant adverse effects reported are proarrhythmias, including TdP. The following are adverse events considered related to therapy, occurring in 1% or more of patients treated with sotalol. Cardiovascular: Bradycardia, dyspnea, chest pain, palpitations, edema, ECG abnormalities, hypotension, proarrhythmia, syncope, heart failure, presyncope. Dermatologic: Rash. Gastro-intestinal: Nausea/vomiting, diarrhea, dyspepsia, abdominal pain, flatulence. Musculoskeletal: Cramps. Nervous/ Psychiatric: Fatigue, dizziness, asthenia, lightheadedness, headache, sleep disturbances, depression, paresthesia, mood changes, anxiety. Urogenital: Sexual dysfunction. Special Senses: Visual disturbances, taste abnormalities, hearing disturbances. Body as a Whole: Fever. In trials of patients with cardiac arrhythmia, the most common adverse events leading to discontinuation of sotalol were fatigue 4%, bradycardia (Cold and cyanotic extremities, Raynaud's phenomenon, increase in existing intermittent claudication and dry eyes have been seen in association with other beta-blockers.

Overdosage

Intentional or accidental overdosage with sotalol has rarely resulted in death. Hemodialysis results in a large reduction of plasma levels of sotalol.
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 g) of sotalol, the following clinical findings were seen: hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia, TdP. If overdosage occurs, therapy with sotalol should be discontinued and the patient observed closely. In addition, if required, the following therapeutic measures are suggested:

Bradycardia: Atropine (0.5 to 2 mg IV), another anticholinergic drug, a beta-adrenergic agonist (isoprenaline, 5 microgram per minute, up to 25 microgram, by slow IV injection) or transvenous cardiac pacing.
Heart Block (second- and third-degree): Transvenous cardiac pacing.
Hypotension: Adrenaline rather than isoprenaline or noradrenaline may be useful, depending on associated factors.
Bronchospasm: Aminophylline or aerosol beta2-receptor stimulant.
TdP: DC cardioversion, transvenous cardiac pacing, adrenaline, and/or magnesium sulphate.

Packaging Information

SOTALAR 40: Blister pack of 10 tablets

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