Sopressor 80 Tablet

Description
White, round tablet, scored on one side, convex with 'SOT' embossed on the other side. Each **Sopressor 80 Tablet** contains Sotalol hydrochloride (HCl) 80 mg.

Pharmacodynamics
Pharmacotherapeutic group: beta blocking agents, non-selective, ATC Code - C07AA07

D,l-sotalol is a non-selective hydrophilic β-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 β-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 β-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
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 occurs to a central (plasma) and a peripheral compartment, with an elimination half-life of 10-20 hours. Sotalol does not bind to plasma proteins and is not metabolised. 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. 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 faeces. Lower doses are necessary in conditions of renal impairment (*see section recommended dose*). Age does not significantly alter the pharmacokinetics, although impaired renal function in geriatric patients can decrease the excretion rate, resulting in increased drug accumulation

Indications
Oral administration of sotalol is indicated for:
- Ventriculararrhythmias:
Treatment of life-threatening ventricular tachyarrythmias; treatment of symptomatic non-sustained ventricular tachyarrhythmias

- Supraventriculararrhythmias:
Prophylaxis of paroxysmal atrial tachycardia, paroxysmal atrial fibrillation, paroxysmal A-V nodal re-entrant tachycardia, paroxysmal A-V re-entrant tachycardia using accessory pathways, and paroxysmal supraventricular tachycardia after surgery; maintenance of normal sinus rhythm following conversion of atrial fibrillation or atrial flutter.

Recommended Dose
The initiation of treatment or changes in dose with **Sopressor 80 Tablet** should follow an appropriate medical evaluation including ECG control with measurement of the corrected QT interval, and assessment of renal function, electrolyte balance, and concomitant medication *(see section Warnings and Precautions).*

As with other antiarrhythmic agents, it is recommended that **Sopressor 80 Tablet** be initiated and doses

increased in a facility capable of monitoring and assessing cardiac rhythm. The dose must be individualised and based on the patient's response. Proarrhythmic events can occur not only at initiation of therapy, but also with each upward dose adjustment.

In view of its beta-adrenergic blocking properties, treatment with **Sopressor 80 Tablet** should not be discontinued suddenly, especially in patients with ischaemic heart disease (angina pectoris, prior acute myocardial infarction) or hypertension, to prevent exacerbation of the disease *(see section Warnings and Precautions).*

Unless otherwise prescribed by the physician, the following guidelines apply:

Method of administration

The following dosing schedule can be recommended:

The initial dose is 80 mg, administered either as a single or as two divided doses of 40 mg at 12 hour intervals, depending on the tablet strength under consideration. Oral dosage of sotalol 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 well 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; however, these doses should only be prescribed when the potential benefit outweighs the increased risk of adverse events, particularly proarrhythmias *(see section Warnings and Precautions).*

Dose in renally Impaired patients:

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

Creatinine clearance (ml/min)	***Adjusted doses***
> 60	Recommended sotalol dose
30-60	½ recommended sotalol dose
10-30	¼ recommended sotalol dose
< 10	Avoid use

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

Men:

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Women: idem x 0.85

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

Dose in hepatically impaired patients

No dose adjustment is required in hepatically impaired patients.

Dose in elderly patients

Old age as such is no reason to adapt the initial dose.

A renal impairment caused by old age may necessitate a dose adjustment (see dose in renally impaired patients).

The tablets should be taken with water half an hour before meals.

Children

Sotalol is not intended for administration to children.

Route of Administration

Oral

Contraindication

Sotalol should not be used where there is:

- evidence of sick sinus syndrome, including sino-atrial block, unless a functioning pace-maker is present
- second and third degree AV heart block unless a functioning pacemaker is present
- congenital or acquired long QT syndromes or drugs associated with possible QT interval prolongation *(see also section Interactions with Other Medicament*s)

- torsades de pointes or drugs associated with it *(see also section Interactions with Other Medicaments*)
- symptomatic sinus bradycardia (≤ 45-50 bpm)
- uncontrolled congestive heart failure, including congestive heart failure of the right ventricle after pulmonary hypertension
- cardiogenic shock
- anaesthesia that produces myocardial depression
- untreated phaeochromocytoma
- hypotension (except due to arrhythmia)
- Raynaud's phenomenon and severe peripheral circulatory disturbances
- history of chronic obstructive airway disease or bronchial asthma
- hypersensitivity to any of the components of the formulation
- metabolic acidosis
- renal failure (creatinine clearance < 10 ml/min)

Warnings and Precautions

Abrupt withdrawal

Hypersensitivity to catecholamines is observed in patients withdrawn from betablocker therapy. Occasional cases of exacerbation of angina pectoris, arrhythmias, and in some cases, myocardial infarction have been reported after abrupt discontinuation of therapy. It is therefore advised that patients are carefully monitored when discontinuing chronically administered sotalol, particularly those with ischaemic heart disease. If possible the dose should be gradually reduced over a period of one or two weeks. If necessary at the same time initiating replacement therapy. Abrupt discontinuation may unmask latent coronary insufficiency. In addition, hypertension may develop.

Proarrhythmias

The most dangerous adverse effect of antiarrhythmic drugs is the aggravation of pre-existing arrhythmias or the provocation of new arrhythmias. Drugs that prolong the QT-interval may cause torsades de pointes, a polymorphic ventricular tachycardia associated with prolongation of the QT-interval. Experience to date indicates that the risk of torsades de pointes 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 torsades de pointes *(see section Interactions with Other Medicaments*). Females may be at increased risk of developing torsades de pointes.

The incidence of torsades de pointes is dose dependent. Torsades de pointes usually occurs early after initiating therapy or escalation of the dose and discontinues spontaneously in most patients. Although most episodes of torsades de pointes are self-limiting or merge symptoms (e.g. syncope) they can progress to ventricular fibrillation.

In clinical trials of patients with sustained VT/VF the incidence of severe proarrhythmia (torsades de pointes 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 torsades de pointes were 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 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. Sotalol should be used with strict caution if the QTc interval exceeds 480 msec 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 the origination of torsades de pointes, however, caution should be exercised regardless of the QTc-interval duration.

Electrolyte disturbances

Sotalol should not be used in patients with hypokalaemia or hypomagnesaemia prior to correction of imbalance; these conditions can exaggerate the degree of QT prolongation, and increase the potential for torsades de pointes. Special attention should be given to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhoea 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. 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. Sotalol should be avoided in patients with left ventricular ejection fractions ≤ 40% without serious ventricular arrhythmias.

Electrocardiographic changes
Excessive prolongation of the QT-interval, >550 msec, can be a sign of toxicity and should be avoided (see Proarrhythmias above). Sinus bradycardia has been observed very commonly in arrhythmia patients receiving sotalol in clinical trials. Bradycardia increases the risk of torsades de pointes. Sinus pause, sinus arrest and sinus node dysfunction occur in less than 1% of patients. The incidence of 2nd- or 3rd-degree AV block is approximately 1%.

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.

Anaesthesia
Sotalol should be used with caution in patients undergoing surgery and where anaesthetics that cause myocardial depression, such as cyclopropane or trichloroethylene are used.

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

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

Renal impairment
As sotalol is mainly eliminated via the kidneys, the dose should be adjusted in patients with renal impairment *(see section Recommended Dose*).

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

Interactions with Other Medicaments
Not recommended associations:
Antiarrhythmics
Class 1a antiarrhythmic drugs, such as disopyramide, quinidine, procainamide and flecainide and other antiarrhythmic drugs such as amiodarone and bepridil are not recommended as concomitant therapy with sotalol, because of their potential to prolong refractoriness (*see section Warnings and Precautions*). The concomitant use of other beta-blocking agents with sotalol 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 torsades de pointes 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 atrioventricular conduction, and ventricular function.

Potassium-Depleting Diuretics
Hypokalaemia or hypomagnesaemia may occur, increasing the potential for torsade de pointes (*see section Warnings and Precautions*).

Other potassium-depleting drugs
Amphotericin B (IV route), corticosteroids (systemic administration), and some laxatives may also be associated with hypokalaemia. Potassium levels should be monitored and corrected appropriately during concommitant 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.

Precautions for use
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 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 methyldopa, 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 hypoglycaemics
Hyperglycaemia may occur, and the dosage of antidiabetic drugs may require adjustment. Symptoms of hypoglycaemia (tachycardia) may be masked by beta-blocking agents.

Neuromuscular blocking agents like tubocurarine
The neuromuscular blockade is prolonged by beta-blocking agents.

Take into account:
Beta-2-receptor stimulants
Beta-agonists may have to be administered in increased dosages when used concomitantly with sotalol.

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 phaeochromocytom and who are treated with sotalol should have their urine screened utilising the HPLC assay with solid phase extraction.

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

Side Effects
If used according to the instructions sotalol is well tolerated by most patients; the most frequent adverse effects arise from its beta-blockade properties. If adverse effects do occur, they usually disappear when the dose is reduced. The most significant adverse effects, however, are those due to proarrhythmia, including torsades de pointes (*see section Warnings and Precautions)*.
The adverse events have been observed in clinical trials and after market launch.

The following definitions apply to the frequencies of adverse reactions:
- Very common (≥ 1/10)

- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)

Psychiatric disorders:
Common: Anxiety, sleep disturbances, mood changes, depression

Nervous system disorders:
Common: Dizziness, light-headedness, headache, paraesthesia, syncope, presyncope, taste abnormalities

Eye disorders:
Common: Visual disturbances
Very rare: Reduced lacrimation

Ear and labyrinth disorders:
Common: Hearing disturbances

Cardiac disorders:
Common: Torsades de pointes, arrhythmia, dyspnoea, chest pain, bradycardia, palpitations, ECG abnormalities, AV-conduction defect, proarrhythmia, heart failure (*see section Warnings and Precautions*)

Vascular disorders:
Common: Hypotension
Not known: Raynaud's disease, aggravation of claudication intermittent, painful cold extremities

Respiratory, thoracic and mediastinal disorders:
Uncommon: In patients with bronchial asthma or a history of asthmatic complaints bronchospasm may occur

Gastrointestinal disorders:
Common: Abdominal pain, nausea, vomiting, diarrhoea, dyspepsia, flatulence, dry mouth

Skin and subcutaneous tissue disorders:
Not known: Rash, exacerbation of symptoms of psoriasis, alopecia, hyperhidrosis

Musculoskeletal and connective tissue disorders:
Common: Muscle cramps

Reproductive system and breast disorders:
Common: Sexual dysfunction

General disorders and administration site conditions:
Common: Fatigue, asthenia, fever, oedema

Blood and Lymphatic system disorders
Not known: Thrombocytopenia

Investigations:
Not known: Formation of antinuclear antibodies has been reported
In trials of patients with cardiac arrhythmia, the most common adverse events leading to discontinuation of sotalol were fatigue 4%, bradycardia (< 50 bpm) 3%, dyspnoea 3%, proarrhythmia 2%, asthenia 2% and dizziness 2%.

Symptoms and Treatment of Overdose
Intentional or accidental overdose with sotalol has rarely resulted in death. Haemodialysis results in a large reduction of plasma levels of sotalol.

Symptoms and treatment
The most common signs to be expected are bradycardia, hypotension, congestive heart failure, bronchospasm and hypoglycaemia. In cases of massive intentional overdose (2-16 g) of sotalol the following clinical findings were seen:
Hypotension, bradycardia, prolongation of QT-interval, premature ventricular complexes, ventricular tachycardia, torsades de pointes.

If overdose occurs, therapy with sotalol should be discontinued and the patient observed closely.

Absorption of sotalol not yet absorbed might be prohibited by gastric lavage, administration of active charcoal and a laxative. Artificial respiration may be necessary.

In addition, the following therapeutic measures are recommended:
Bradycardia: Atropine (0.5 to 2 mg i.v.), another anticholinergic medicinal product, a beta-adrenergic agonist (isoprenaline, 5 micrograms per minute, up to 25 micrograms, by slow i.v. 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 beta-2-receptor stimulant (aerosol)
Torsades de pointes: Cardioversion, transvenous cardiac pacing, adrenaline, and or magnesium sulphate

Effects on Ability to Drive and Use Machine
There are no data available, but the occasional occurrence of side-effects such as dizziness and fatigue should be taken into account *(see section Side Effects*)

Storage Condition
Store in a cool dry place, below 30°C. Protect from light.
Shelf life: Please refer to the outer box label.

Packing
Blister of 10 and 25 tablets each.
Box of (10 x10 tablets) and (4 x 25 tablets).

Revision date: February 2022

Keep medicines out of reach of children. ***Jauhi daripada kanak-kanak.***

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