# Etizem

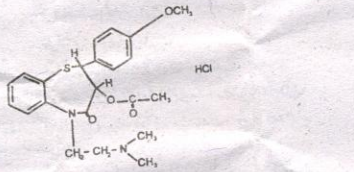
(Diltiazem Hydrochloride)

**SR Capsules 90 mg.**

**Tablets 30 mg / 60 mg.**

## DESCRIPTION

Diltiazem Hydrochloride is a synthetic calcium antagonist. The chemical structure of Diltiazem Hydrochloride is unrelated to that of the calcium antagonists. It is a derivative of benzothiazepine. The structural formula is as follows.




The active form is the Hydrochloride of cis form of the dextrogyrated isomer. Molecular formula:C22 H26 N2 O4 S.HCl Molecular weight:450.98 **Etizem SR** capsules contain Diltiazem Hydrochloride as sustained release pellets. Etizem tablets contain Diltiazem Hydrochloride as an active ingredient.

## INDICATIONS

Angina Pectoris due to Coronary Artery Spasm: **Etizem** is indicated in the treatment of angina pectoris due to coronary artery spasm. Diltiazem has been shown to be effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).

Chronic Stable Angina (Classic Effort-associated Angina):**Etizem** is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. Diltiazem has been effective in short term controlled trials in reducing angina frequency and increasing exercise tolerance but confirmation of sustained effectiveness is incomplete.

There are few controlled studies on the effectiveness of the concomitant use of diltiazem and beta blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

**Hypertension: Etizem** is indicated in the treatment of essential hypertension as a single agent or in combination with other agents. **Etizem** is particularly useful when angina and hypertension occur in the same patient.

Mechanisms of Action: Although precise mechanisms of its antihypertensive and antianginal actions are still being delineated. **Etizem** is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: Etizem is a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine induced coronary artery spasm are inhibited by **Etizem**.

2. Exertional Angina: **Etizem** produces increase in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reduction in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

3. Hypertension: **Etizem** causes a decrease in peripheral vascular resistance and a fall in blood pressure. Since significant negative inotropic effect has not been found, the blood pressure lowering effect is thought to be mainly due to peripheral vasodilation.

In a study involving single oral doses of 300 mg of diltiazem in six normal volunteers, the average maximum PR prolongation was a 14% with no instances of greater than first degree AV block. Diltiazem associated prolongation of the AH interval is not more pronounced in patients with first degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (upto 50%

Chronic oral administration of diltiazem in doses of upto 240 mg/day has resulted in small increases of PR interval, but has not usually produced abnormal prolongation.

## PHARMACOKINETICS

The principal effect of **Etizem** is on inhibited transmembrane calcium flux in the cells of the myocardium and of vascular wall smooth muscle, thereby reducing the oxygen demand of myocardium and relaxing the arteries. The resulting dilation leads to a reduction of peripheral resistance and of arterial blood pressure. Diltiazem is absorbed from the tablet formulation to about 80% of the reference capsule and is subject to extensive first pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. Diltiazem undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown that diltiazem binding is not altered by therapeutic concentrations of digoxin,hydrochlorthiazide, phenylbutazone, propranolol, salicyclic acid or warfarin. Single oral dose of 30 to 120 mg of diltiazem results in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration.The plasma elimination half life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of diltiazem appear to be in the range of 50-200 ng/ml. There is a departure from dose linearity when single doses above 60 mg are given: a 120 mg dose gave blood levels three times that of 60 mg dose. The pharmacokinetics of diltiazem and its major metabolite, desacetyl diltiazem in patients with severly impaired renal function were similar to those with normal renal function. Once the capsules are opened, the micro granules are distributed over a large part of the digestive tract, thus increasing the area of contact between the active principle and the digestive juices. This improves the absorption and enhances the distribution of the medicine. The sustained release formulation has several benefits. It reduces the number of daily doses by prolonging the release of active ingredient and obtain an effect which would remain stable for several hours by means of a plasma concentration curve. Moreover, it decreases the side effects caused by excessively high plasma levels, by lowering peak concentration.

**Etizem** tablet is rapidly absorbed from the intestine in man, giving the absolute bioavailability. It appears in the blood, 30 minutes after oral administration.

## CONTRA INDICATIONS

Treatment with **Etizem** is generally well tolerated. Care should be taken while administering to the following patients :

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pace maker.
2. Patients with second or third degree Atrio-ventricular block except in the presence of a functioning ventricular pace maker.
3. Patients with hypotension (less than 90 mm Hg systolic).
4. Patients who have demonstrated hypersensitivity to the drug.
5. Patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.
6. **Etizem** should not be recommended in pregnant women and children, as the safety of **Etizem** has not been established.

## WARNINGS:

Cardiac Conduction: Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second or third degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effect on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds)after a single dose of 60 mg of diltiazem.

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of diltiazem alone or in combination with beta blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.

Hyptotension: Decrease in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

Acute Hepatic Injury: In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in most cases, but probable in some (see precautions).

## PRECAUTIONS

1. **Etizem** has an antihypertensive effect, when used with other antihypertensive agents. Therefore, the dosage may need to be adjusted when adding one to the other.
2. General: **Etizem** (ditiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. Dermatological events may be transient and disappear, however, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported.
3. Dermatological events may be transient and may disappear, despite continued use of **Etizem** should a dermatological reaction persist, the drug must be discontinued.
4. Drug interaction: Pharmacological studies indicate that there may be additive effects in prolonging AV conduction when using beta blockers or digitalis1, concomitantly with diltiazem (see warnings). Controlled and uncontrolled studies suggest that concomitant use of diltiazem and beta blockers or digitalis is usually well tolerated. Available data are not sufficient however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers diltiazem has been shown to increase serum digoxin levels up to 20%. Concomitant administration of cimetidine has been shown to increase diltiazem levels. The depression of cardiac contractility, conductivity and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. Carcinogenesis, Mutagenesis, Impairment of Fertility: A 24-month study in rats and a 21 months study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in-vitro bacterial tests. No intrinsic effect on fertility was observed in rats.
5. Withdrawls: In case of withdrawl, reduce the dose gradually and observe the symptoms carefully. **Etizem** should not be discontinued without a Physician's directions.
6. When used concomitantly, anatesthetic agents and **Etizem** dose should be titrated carefully.
7. **Pregnancy:** Category C. Reproduction studies have been conducted in mice, rats and rabbits. Administration of doses ranging form five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well controlled studies in pregnant women therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the foetus.

**Nursing Mothers:** Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of Etizem is deemed essential, an alternative method of infant feeding should be instituted.

8. Paediatric use: Safety and effectiveness in children have not been established.

**ADVERSE REACTION:**

Serious adverse reactions have been rare in studies carried out to date but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In placebo-controlled trials the incidence of adverse reactions reported during diltiazem therapy was not greater than reported during placebo therapy.

The following represent occurrence observed in clinical studies which can be at least reasonable with the pharmacology of calcium influx inhibition. In many cases, the relationship to diltiazem has not been established. The most common occurrences as well as their frequency of presentation are: oedema (2.4%), headache 2.1%, nausea (1.9%) dizziness (1.5%) rash (1.3%), asthenia (1.2%) in addition the following events were reported infrequently (less than 1%).

**Cardiovascular:** Angina, Arrhythmia, AV block (first degree) AV block (Second or third degree-see conduction warning) bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.

**Nervous system:** Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

**Gastrointestinal:** Anorexia, constipation, diarrhoea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT,and LDH, vomiting, weight increase.

**Dermatologic:** Petechiae, pruritus, photosensitivity, urticaria. Other: Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

**OVER DOSAGE OR EXAGGERATED RESPONSE:**
Over dosage experience with oral diltiazem has been limited. Single oral dose of 300mg of diltiazem have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered.

**Bradycardia:** Administer atropine (0.6o to 1.0 mg). If is no response to vagal blockade, administer isoproterenol cautiously.

High Degree AV Block: Treat as for bradycardia above: Fixed high degree AV block should be treated with cardiac pacing.

**Cardiac Failure:** Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension: Vasopressors (e.g. dopamine or levarterenol bitartarate). Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD50's in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD50's in these species were 60 and 38 mg/kg, respectively. The oral LD50's in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known. Due to extensive metabolism blood levels after a standard dose of diltiazem can very over ten folds, limiting the usefulness of blood levels in over dose cases. Over doses as much as 10.8 gram of oral diltiazem have been survived following appropriate supportive care.

**DOSAGE AND ADMINISTRATION**
Dosage is dependent on patient's condition and strength prescribed. To ensure the efficacy and obtain the desired results, physician's direction should be strictly followed.

Dosage is adjusted to each patient's needs. Dose titration in patients with impaired hepatic or renal function should be carried out with particular caution.

For Hypertension: Initial dose is 30 mg three times daily which may be increased gradually at two intervals, if necessary, to a maximum of 120mg three times daily.

**For Angina:** Initial dose is 30 mg three times daily, which may be increased gradually at one to two days intervals, if necessary, to a maximum of 120 mg three times daily.

Concomitant use with other Antianginal agents and Antihypertensive agents:

1. Sublingual NTG may be taken as required to abort acut anginal attacks during **Etizem** therapy.

2. Prophylactic Nitrate Therapy-**Etizem** may be safel coadministered with short and long acting nitrates, but ther have been no controlled studies to evaluate the antiangina effectiveness of this combination.

3. Beta Blockers- (see Precautions).

4. **Etizem** should not be used with other calcium antagonists.

5. **Etizem** may be used with other groups of antihypertensive such as diuretics and ACE inhibitors. Generally one capsule of **Etizem** 90 mg twice daily is recommended.

**PHARMACEUTICAL PRECAUTIONS**

Store below 25°C. Protect from light.
Keep out of the reach of children.
To be dispensed only on the prescription of a registered practitioner.

**PRESENTATION**

**Etizem SR** capsules 90 mg in a pack of 20 capsules.
**Etizem** 60 mg tablets in 3x10's blister strips in carton.
**Etizem** 30 mg tablets 3x10's blister strips in carton.

Manufactured by:
**Searle Pakistan Limited,**
F-319 S.I.T.E., Karachi.
For : **ICI Pakistan Limited,**
Life Sciences Business, Pharmaceuticals Division,
5-West Wharf Karachi Pakistan.

# ایٹیزم

## پیشکش :

ایٹیزم - ایس آر کیپسول میں ڈلٹائزم ہائیڈروکلورائیڈ (ایس آر۔ پیلٹس) شامل ہے ،
ایٹیزم ٹیبلیٹس میں ڈلٹائزم ہائیڈروکلورائیڈ شامل ہے۔
ایٹیزم - ایس آر کیپسول مندرجہ ذیل طاقتوں میں دستیاب ہیں۔
ایٹیزم - ایس آر ۹۰ ملی گرام - ۲۰ کیپسول فی پیک
ایٹیزم - ۳۰ ملی گرام - ۳۰ ٹیبلیٹس فی پیک
ایٹیزم - ۶۰ ملی گرام - ۳۰ ٹیبلیٹس فی پیک
ایٹیزم - ایس آر کیپسول کا سست دستیابی کا فارمولا کئی فوائد رکھتا ہے۔ سُست دستیابی کی وجہ سے کسی بھی وقت خون میں دوا کی مقدار ضرورت سے زیادہ موجود نہیں ہوتی جس کی وجہ سے نقصان کا احتمال نہیں ہے۔ دوا کی سُست دستیابی کی وجہ سے روزانہ کی خوراک کی تعداد میں بھی کمی ہو جاتی ہے۔
ایٹیزم ٹیبلیٹس کی خوراک ۲۰ منٹ کے اندر دورانِ خون میں شامل ہو جاتی ہے اور فوری اثر دکھاتی ہے

## خوراک اور طریقہ استعمال :

ایٹیزم کی خوراک کا تعین مریض کی کیفیت اور دوا کی طاقت کے حساب سے کیا جاتا ہے بہترین نتائج حاصل کرنے کے لئے معالج کی ہدایات پر سختی سے عمل کرنا چاہیئے۔ عموی خوراک کے طور پر ایٹیزم - ایس آر ۹۰ ملی گرام کا ایک ایک کیپسول صبح و شام روزانہ کافی ہے۔ عموی خوراک کے طور پر ایٹیزم ٹیبلیٹس ۳۰ ملی گرام دن میں تین بار اور ۶۰ ملی گرام دن میں دو بار ہے۔ خون کا دباؤ کم کرنے والی دیگر ادویات کے ساتھ خوراک کی مقدار میں تبدیلی کی جا سکتی ہے۔ ایٹیزم - ایس آر کیپسول / ٹیبلیٹس ہمیشہ سالم نگلنا چاہیئے۔ چبانا یا کھول کر استعمال کرنا دوا کے اثر کو کم کرتا ہے۔

## ممنوعات و احتیاط :

دوا ہمیشہ صرف معالج کی ہدایات کے مطابق استعمال کریں۔
دوا کو ایک دم ترک کرنے کے بجائے آہستہ آہستہ کم کرنا چاہیئے اور اس دوران مریض کی حالت کا بغور مشاہدہ کرنا ضروری ہے۔
حاملہ دودھ پلانے والی خواتین اور بچوں میں دوا کا استعمال ممنوع ہے۔
مزید تفصیلات کے لئے انگریزی حصہ پڑھیں۔
۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت میں رکھیں۔
روشنی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔