Apuzin® Tablet 25 mg

Captopril is the first of the new class of antihypertensive agents- the angiotensin converting enzyme (ACE) inhibitors. It is a specific competitive inhibitor of angiotensin I to angiotensin II. Chemically, it is known as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. Captopril is also effective in the management of heart failure.

Active Ingredient(s):
Each tablet contains:
Captopril 25mg

Pharmacodynamics:
1. The beneficial effects of Captopril in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. Reduction of angiotensin II leads to aldosterone secretion and, as a result, small increase in serum potassium may occur along with sodium and fluid loss. Captopril prevents the convertion of angiotensin I to angiotensin II by inhibition of ACE.

Pharmacokinetics:
1. After oral administration of therapeutic doses of Captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40%, Captopril therefore should be given one hour before meals.
2. Approximately 25 to 30% of the circulated drug is bound to plasma protein. The apparent elimination half-life of Captopril metabolite in blood is probably less than 3 hours. In patients with renal impairment, retention of unchanged Captopril occurs.
3. In a 24-hour period, over 95% of the absorbed dose is eliminated in the urine; 40~50% is unchanged drug; most of the remainder is the disulfide dimer of Captopril and Captopril-cysteine disulfide.

Indication(s):
1. Hypertension: It may be used alone or in combination with other antihypertensive agents, especially thiazide type diuretics. There is an additive effects on lowering blood pressure when combined Captopril and thiazide are used.
2. Congestive heart failure: For patients who have not responded adequately to treatment with diuretics and digitalis.
3. Following myocardial infarction.
4. Diabetic nephropathy.

Dosage and Administration:
Apuzin® tablet should be taken one hour before meals.

Hypertension:
The initial dose of Apuzin® is one tablet (25mg) *b.i.d.* or *t.i.d.* If satisfactory reduction of blood pressure has not been achieved after one or two weeks, the dose may be increased to 50mg *b.i.d.* or *t.i.d.* The usual dose range is 25 to 150mg b.i.d. or t.i.d. A maximum daily dose of 450mg Apuzin should not be exceeded.

Heart Failure:
The usual daily dosage is 25mg *t.i.d.* After a dose of 50mg *t.i.d.* is reached, further increases in dosage should be delayed, where possible, for at least two weeks to determine if a satisfactory response occur. According to experience, most patients have had a satisfactory clinical improvement at 50 or 100mg *t.i.d.* A maximum daily dose of 450mg of Apuzin should not be exceeded.

Myocardial Infarction:
After an initial dose of 6.25mg, therapy should be increased to 37.5mg daily in divided doses as tolerated. Captopril should then be increased as tolerated to 75mg a day in divided doses during the next several days and to a final target dose of 150mg daily in divided doses over the next several weeks.
If symptomatic hypotension occurs, a dosage reduction may be required. Subsequent attempts at achieving the target dose of 150mg should be based on the patient's tolerance to Captopril. Captopril may be used in patients treated with other post-myocardial infarction therapies, thrombolytics, aspirin, β-blockers.

Diabetic Nephropathy:
Recommended daily dose: 75-100mg in divided doses.

Dosage adjustment in renal impairment:
For patients with significant renal impairment, initial daily dosage of Apuzin® should be reduced, a smaller increments utilized for titration, which should be quite slow (1 to 2 weeks interval). After the desired therapeutic effects have been achieved, the dose should be slowly back-titrated to determine the minimal effective dose.
To be dispensed on physician's prescription.

Route of administration: Oral

Contraindication(s):
1. Captopril is contraindicated in patients who are hypersensitive to this product or any other angiotensin converting enzyme inhibitor.
2. Captopril is contraindicated in Pregnancy. It can cause fetal and neonatal morbidity and death when administered to pregnant women.
   FDA Pregnancy Category C : First Trimester.
   FDA Pregnancy Category D : Second and Third Trimester.

Precaution(s) / Warning(s):

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY

1. Proteinuria may occur by the eighth month of therapy especially in patients with a history of renal disease. In most cases, proteinuria subsides or clear within 6 months whether or not Captopril is continued. In patients who develop proteinuria exceeding 1g/day or proteinuria that is increasing, the benefits and risks of continuing Captopril should be evaluated.
2. In patients with collagen vascular disease (eg. systemic lupus erythematous, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinicals trial. If Captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-weeks intervals for about 3 months, then periodically.
3. All patients treated with Captopril should be told to report any signs of infections (e.g. sore throat, fever). If infection is suspected, white cell counts should be performed without delay. Discontinuation of Captopril and other drug has generally led to prompt return of the white cell count to normal.

4. Because of the potential fall in the blood pressure in patients with heart failure (with blood pressure either normal or low), therapy should be started under close medical supervision, at least one hour after the initial dose. If hypotensive occurs, the patients should be placed in supine position and, if necessary, receive an IV infusion of normal saline. This transient hypotensive response is not contraindicated to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.
5. Some patients with renal diseases, particularly those with severe renal artery stenosis, have developed increased in BUN and serum creatinine after reduction of blood pressure with Captopril.
6. Captopril may caused false-positive reactions to urinary acetone and for dipstick tests for urinary ketones.
7. In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Captopril blocks angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.
8. Captopril is excreted in breast milk, with the concentration approximately 1% of maternal blood concentration. There is potential serious adverse reaction in the nursing infants, therefore risk-benefit of the use of captopril in nursing should be considered.
9. In pediatrics use, there is risk of oliguria and neurologic abnormalities. Safety and effectiveness in children have not been established.

Drug Interaction(s):
1. Concurrent administration of potassium sparing diuretic with ACE inhibitors may result in hyperkalemia.
2. ACE inhibitor may interact with other antihypertensive to produce additive hypotensive effects.
3. Concurrent use of NSAIDs, especially indomethacin may antagonise the antihypertensive effects of ACE inhibitors.
4. Captopril may reduce excretion of lithium, causing increased plasma-lithium concentration.

Pregnancy And Lactation:

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY

Captopril is excreted in breast milk, with the concentration approxiamately 1% of maternal blood concentration. There is potential serious adverse reaction in the nursing infants, therefore risk-benefit of the use of captopril in nursing should be considered.

Side Effect(s) / Adverse Reaction(s):

Renal:	Proteinuria, transient elevation of BUN and creatinine, and hyperkalemia.
Hematologic:	Neutropenia.
Dermatologic:	Rash often with pruritus, and sometimes with fever and eosinophilia. It is usually maculopapular, and rarely urticarial during the first 4 weeks of therapy. The rash is usually mild and disappears within a few days of dosage reduction. Pemphigoid-like lesion and photosensitivity may also occur but may disappear upon discontinuing of therapy.
Cardiovascular:	Hypotensive may occur in congestive heart failure, renin-dependent hypertension or serious volume depleted patients. Tachycardia may also occur in volume depleted patients.
Gastrointestinal:	Patients develop a diminution or loss of taste perception. Taste impairment is reversible or usually self-limited (2~3 months). Weight loss may be associated with the loss of taste. Some patients may develop aphthous ulcers, gastric irritation or abdominal pain.
Others:	Paresthesias, serum sickness, cough, bronchospasm and lymphadenhypertrophy.

Effects on Ability to Drive and Use Machine
As with other antihypertensives, the ability to drive and use machines may be reduced, namely at the start of the treatment, or when posology is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

Symptoms and Treatment for Overdosage, and Antidote(s):
Symptoms of overdosage includes hypotension (dizziness, lightheadedness, or fainting) and angioedema with swelling of the extremities, face, mouth and lips.
In the event of overdosage, correction of hypotension would be of primary concern. Volume expansion with IV infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

Storage Condition(s):
Store at temperature below 30ºC. Protect from light and moisture.

Shelf-Life:
3 years from the date of manufacture.

Product Description and Packing(s):
A white square tablet, one side impressed with “  ”.

Blister packing of 10’s x 10, 10’s x 50 and 10’s x 100.

Y. S. P.®
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