CAPOZIDE®

SB

Captopril 50 mg /hydrochlorothiazide 25mg

TABLETS

DESCRIPTION

Capozide is a combination of captopril, designated chemically as l-[(2S)-3-mercapto-2-methlpropionyl]-L-proline, a specific competitive inhibitor of angiotensin I-converting enzyme, the enzyme responsible for the conversion of angiotensin I to angiotensin II, and hydrochlorothiazide, a benzothiadiazine(thiazide) diuretic-antihypertensive agent. Captopril and a diuretic have been shown to be of benefit in the treatment of hypertension and the management of heart failure.

EXCIPIENTS

Avicel, Starch, Color F D & C yellow, Magnesium Stearate, Stearic Acid, Lactose.

PHARMACOLOGY

The beneficial effects of captopril in hypertension and heart failure appear to result primarily from suppression of the rennin-angiotensin-aldosterone system. However, no consistent correlation between renin levels and response to the drug has been demonstrated. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide.

Angiotensin I is then converted enzymatically by angiotensin-converting enzyme (ACE) to the octapeptide angiotensin II, one of the most potent endogenous vasoconstrictor substances. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retension and potassium loss.

Captopril prevents the conversion of angiotensin I to angiotensin Ii by inhibition of ACE and this is reflected by a decrease in the pressor substance, angiotensin II, and increase in plasma rennin, activity (PRA). The latter is due to the relative lack of negative feedback on renin release caused by reduction in angiotensin II.

Decreased concentrations of aldosterone are found in blood and urine, and as a result,

small increase in serum potassium may occur along with sodium and fluid loss. Increased concentrations of bradykinin or prostaglandin E2 may also have a role in the therapeutic effect of captopril.

Hydrochlorothiazide is a thiazide diuretic which increases excretion of sodium and chloride in approximately equivalent amounts. Natiuresis causes a secondary loss of potassium and bicarbonate.

With diuretic treatment, blood pressure and blood volume fall resulting in a rise in angiotensin II levels which tend to blunt the hypotenive effect. Captopril blocks this rise in angiotensin II. Since captopril and hydrochlorothiazide lower blood pressure by different, though complementary mechanisms, their antihypertensive effects are additive, and, concurrent administration may permit the use of lower doses of each drug. Because captopril reduces the production of aldosterone, its combination with hydrochlorothiazide may also minimize diuretic induced hypokalemia.

Following oral administration of captopril, rapid absorption occurs with peak blood levels at about one hour. The average minimal absorption is approximately 70-75 percent. Although the presence of food in the gastrointestinal tract reduces the absorption of captopril, this does not appear to substantially reduce its antihypertensive efficacy. Only 25 to 30 percent of the drug is bound to plasma proteins. After administration of a radiolabeled oral dose, the apparent elimination half-life for total radioactivity in blood is about 12 hours for the 12 to 48-hours time interval. The half-life of unchanged drug is approximately 2 hours, however the therapeutic effects of the drug persist for a longer period of time than does demonstrable inhibition of serum-ACE.

About 70 to 75 percent of a dose of captopril is excreted in the urine (of which 50 percent is unchanged drug and the remainder conjugates with endogenous thiol compounds [e.g.,captopril cysteine]and the disulfide dimer of the parent compound).

Oral absorption of hyrochlorothiazide is relatively rapid. Diuretic action occurs within 2 hours of administration with peak effect in in about 4 hours persisting for approximately 6 to 12 hours.

Thiazides are rapidly eliminated by the kidney.

Captopril produces a reduction in peripheral arterial resistance in hypertensive patients with either no change or an increase in cardiac output. Clinically significant reductions of blood pressure are often observed 60 to 90 minutes or sooner after oral absorption of captopril.

The reduction in blood pressure is usually progressive ant to achieve maximal therapeutic effects of a given dosage regimen, several weeks of administration may be required. Orthostatic effects and tachycardia are in frequent, occurring particularly in volume depleted patients.

No sudden increase in blood pressure after withdrawal of the drug has been demonstrated. The effects of captopril and of thiazide diuretics on the renin-angiotensin-aldosterone system are complementary. Unlike treatment with thiazide diuretics, treatment with captopril is not associated with increases in serum cholesterol and serum uric acid concentrations or with decreases in serum potssium values.

Treatment with captopril may induce regression of left ventricular hypertrophy in hypertensive patients.

Heart failure patients treated with captopril demonstrate increases in exercise time, ability to perform at higher workloads, and improvement in functional capabilities by New York Heart Association criteria.

In patients with frequent ventricular premature beats or ventricular couplets, treatment with captopril has been shown to decrease the frequency of these arrhythmias compared to treatment with digitalis. Hemodynamic changes observed in heart failure patients treated with captopril include reduction of preload (left ventricular end-diastlic volume) and reduction of afterload (left ventricular wall stress- a product of vascular resistance and ventricular size) resulting in increase in cardiac output. Heart rate generally remains unchanged or decrease, and blood pressure may decrease, especially acutely (see WARNINGS). Treatment with captopril lowers plasma concentrations of aldosterone, conserves potassium, and may, in conjunction with furosemide therapy, correct hyponatremia

associated with heart failure. The beneficial, clinical, hemodynamic and biochemical effects of captopril occur promptly and persist. Evidence from studies in patients with severe heart failure suggests that treatment with angiotensin-enzyme inhibitors ma y prolong survival.

Abrupt cardiac decompensation has not been seen with sudden withdrawal of captopril therapy.

Studies have demonstrated an acute increase in renal blood flow after administration of captopril. Glomerular filtration rate is usually unchanged. In a large, long-term clinical trial, captopril was found to preserve renal function both in patients with and without abnormal serum creatinine values at stud entry. In instances of rapid reduction of long-standing or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, resulting in transient rises in serum creatinine and urea nitrogen

Most studies in laboratory animals indicate that captopril does not cross the blood-brain barrier in significant amounts.

An increase in cerebral blood flow after captopril has been found in spontaneously hypertensive rats. Increases or maintenance of cerebral blood flow have been demonstrated in patients with congestive heart failure despite decreases in blood pressure.

INDICATIONS

HYPERTENSION: CAPOZIDE is indicated for the treatment of patients with hypertension and may be used alone or in combination with other antihypertensive agents.

HEART FAILURE: CAPOZIDE is indicated for the maintenance treatment of patients with heart failure.

CONTRAINDICATIONS

CAPOZIDE is contraindicated in patients with anuria or a hypersensitivity to captopril, thiazides, or any sulfonamide-derived drug.

WARNINGS

(See also DRUG INTERACTIONS)

Neutropenia has occurred in some patients in clinical studies usually within three months of initiation of captopril therapy.

This phenomenon has essentially y been limited to those who had pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy, or a combination of these complicating factors. Thus, for patients with impaired renal function, collagen vascular disease, or who are receiving immunosuppressant drugs, white blood cell and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of CAPOZIDE therapy and periodically thereafter. If the neutrophil counts falls below 1000/mmD, CAPOZIDE should be discontinued and the patient's course should not be followed.

All patients receiving CAPOZIDE should be told to report any signs of infection (e.g. sore throat, fever).

Serious infections resulting from the neutropenia and which proved fatal in a few cases usually occurred only in patients with impaired renal function.

The combination tablet should not be used to initiate therapy for heart failure. Once the optimal doses of captopril and hydrochlorothiazide have been established CAPOZIDE may be substituted.

Hypotension may occur, particularly in patients who are receiving aggressive diuretic therapy, or who have either severe, rennin dependant hypertension (e.g.renovascular hypertension), or severe congestive heart failure. In these patients, exaggerated hypotensive responses have occurred, usually within one hour of the initial dose of captopril but sometimes after any one of the first several doses. Hypotesion is usually transient and well tolerated, producing either no symptoms or brief mild lightheadedness; although in rare instances it has been associated with arrytmia or conduction defects. The possibility of this occurrence can be lessened in these patients by discontinuing diuretic therapy or significantly reducing the diuretic dose for 4 to 7 days prior to initiating CAPOZIDE therapy.

By commencing CAPOZIDE therapy with small doses, the duration of any hypotensive effect is reduced.

It is recommended that patients at risk of experiencing exaggerated responses initiate CAPOZIDE therapy under medical supervision.

A hypotensive episode following the initial dose of CAPOZIDE does not preclude further titration of the drug.

Proteinuria has been seen in less than one percent of patients receiving captopril, but this has predominantly in those who had prior renal disease. Although membranous glomerulopathy was found in biopsies taken from some proteinuric patients, a casual relationship to captopril has been established. For patients with prior renal disease, urinary protein estimations (dipstick) should be done prior to treatment and periodically thereafter.

Fetal/Neonatal Morbidity and Mortality: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOZIDE should be discontinued as soon as possible.

PRECAUTIONS

Patients with renal disease, particularly those with bilateral renal artery stenosis may develop increases in blood urea nitrogen and serum creatinine after reduction of blood pressure with captopril usually administered along with a diuretic. CAPOZIDE, therefore would not be appropriate for patients with severe renal impairment since loopb diuretic (e.g. furosemide) rather than a thiazide are preferred for such patients. Azotemia may be induced by thiazides in patients with impaired renal function. Some patients with heart failure have experienced a reduction in renal function during long-term treatment with captopril that usually stabilized at the reduced level. In patients with impaired renal function cumulative effects of thiazide may develop.

CAPOZIDE should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

A few patients with captopril have developed angioedema of the face, mucous membranes of the mouth, and the extremities which is reversible on discontinuation of the drug. Laryngeal edema and anaphylaxis have also been reported.

CAPOZIDE, as with any drug that reduces vascular resistance, should be used only with extreme caution in patients with aortic stenosis because of the potentially harmful consequences of reduced coronary perfusion secondary to the reduced blood pressure.

Patients receiving CAPOZIDE should be observed for clinical signs of thiazide induced fluid or electrolyte imbalance.

Hyperkalemia, should it occur, can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Because captopril reduces the production of aldosterone, its combination with hydrochlorothiazide may minimize the diuretic-induced hypokalemia. However, some patients may still require potassium supplements.

Hyperuricemia may occur or frank gout may be precipitated by thiazides in certain patients. Insulin requirements in diabetic patients may be altered b thiazides and latent diabetes mellitus may emerge.

Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients during prolonged thiazide therapy.

A rise in serum cholesterol has been noted after use of diurteics.

Sensitivity reactions to thiazide may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide therapy.

Female patients of childbearing age should be told about the consequences of second-and third-trimester exposure to ACE inhibitors, and that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester.

Women should be instructed to notify their physician immediately if pregnancy is suspected.

PREGNANCY

Pregnancy: Categories C(first trimester) and D (second and third trimester). See WARNINGS: Fetal/Neonatal Mortality and Morbidity.

Captopril:
Captopril was embryocidal in rabbits when given in doses about 2 to 7 times (on a mg/kg basis) the maximum recommended human dose and low incidence of craniofacial malformations were seen. These effects in rabbits were most probably due to the particularly marked decrease in blood pressure caused b the drug in this species.
Captopril given to pregnant rats at 400 times the recommended human dose continuously during gestation and lactation caused a reduction in neonatal survival.
No teratogenic effects (malformations) have been observed after large doses of captopril in hamsters and rats. Captopril crosses the human placenta.
Hydrochlorothiazide:
Teratology studies have been performed in pregnant rats using captopril and hydrochlorothiazide individually u and in combination; each agent was administered in doses up to 1350mg/kg (400 times the maximum recommended human dose for hydrochlorothiazide). In this species no evidence of embryotoxicity, fetotoxicity, or tertaogenicity was found in any group; however animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies of captopril or CAPOZIDE in pregnant women, there have been published reports of hypotension, anuria, and intrauterine growth retardation in a few neonates whose mothers received captopril during pregnancy, CAPOZIDE should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit justifies a potential risk to the fetus.

NURSING MOTHERS
Small amounts of captopril and thiazides are excreted in the human breast milk. Therefore, breast feeding should be avoided.

SURGERY/ANASTHESIA
In patients undergoing major surgery or during anesthesia CAPOZIDE may cause hypertension which can be corrected b volume expansion.

ADVERSE REACTIONS
CAPTOPRIL:
Captopril is well tolerated in patients with uncomplicated, essential hypertension. As assessed by well established psychometric tests, captopril does not comprise the patient's quality of life. Among a large group of hypertensive men, treatment with captopril was associated with either an improvement or no change in measurements of general well-being, work performance, cognitive functioning, sexual dysfunction, sleep dysfunction, life satisfaction and social participation. Incidences of adverse reactions shown on the table below are based on results from clinical trials of 8 to 16 weeks duration in patients with normal renal function with uncomplicated, mild to moderate hypertension. The total daily doses of captopril were 100 mg or less. Many of these untoward events were also reported in patients who received placebo.

Reactions reported less frequently in this population included chest pain, orthostatic hypotension, palpitations, pruritus, anorexia, weight loss, and joint pain/ swelling. Cough, depression, muscle cramps, and transient ischemic attacks, were reported in one patient each.
The rash associated with captopril is usually pruritic and maculopapular, rarely urticarial. It generally occurs during the first month of treatment, and is usually self-limited and reversible, it may respond to antihistamine therapy. In the majority of patients the rash resolves with continuation of therapy at the same or reduced dosage. Taste impairment is reversible and usually self-limited (2-3 months). In most patients the condition resolves with the continuation of therapy at the same or reduced dosage. Stomatitis, resembling aphthous ulcers, has been reported.

MILD TO MODERATE, UNCOMPLICATED HYPERTENSION CAPTOPRIL
(N=1174)

REACTION	Percent of Patients Experiencing Reaction
Headache	5.5
Rash	3.7
Dizziness	3.5
Nausea	3.2
Fatigue/Malaise	3.1
Taste Alteration	1.5
Gastric Upset	1.4
Diarrhea	1.1

The additional reactions listed below were reported in earlier clinical trials (commonly utilizing total daily doses of captopril in excess of 100 mg), or were identified post marketing. Many of these patients had significant underling illnesses and/or were receiving other medications; some had risk factors that are identified in the WARNINGS and PRECAUTIONS sections.
Cardiovascular:
Hypotension may occur after initiation of captopril therapy in patients with heart failure, rennin-dependant hypertension or who are significant volume-depleted (see WARNINGS). Hypotension and acute renal dysfunction have been reported in patients receiving captopril who became dehydrated due to incidental causes. Tachycardia has been observed in volume-depleted patients.
Respiratory:
A dry cough, reversible upon discontinuation of captopril may be observed. Dyspnea has been reported. Pulmonary infiltrates have been reported very rarely.
Dermatologic:
toxic epidermal necrolysis. Stevens-Johnson syndrome, angioedema (see PRECAUTIONS), alopecia, reversible pemphigoid-like lesion, photosensitivity and flushing have been reported.
Gastrointestinal:
Rare cases of hepatocellular injury with or without cholestisis have been reported. Elevation of liver enzyme value has been reported, although the casual relationship to captopril therapy is unclear. Gastric irritation and abdominal pain have been reported.
Hematologic:
neutropenia, agranulocytosis has occurred (see WARNINGS). Cases of anemia including hemolytic anemia, thrombocytopenia, and pancytopenia have been reported.

Renal: proteinuria including reports of the nephritic syndrome (see WARNINGS). Renal failure, elevations of BUN and creatinine values have occurred (see PRECAUTIONS).
Increase in serum potassium and decreases in serum sodium concentrations, acidosis, urinary frequency, and oliguria have been observed.
Other: Anaphylaxis, laryngeal edema (see PRECAUTIONS), serum sickness, bronchospasm, paresthesias, and lymphadenopathy have been reported. Positive ANA titres and eosinophilia, sometimes associated with rash, have been observed. Pancreatitis and peripheral neuropathy have been reported rarely.

HYDROCHLOROTHIAZIDE:
Gastrointestinal Sytem: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intahepatic cholestatic jaundice), pancreatitis, and sialadenitis. Central nervous System: Dizziness, vertigo, pancreatitis, and xanthopsia.
Hematologic: Leukopenia, agranulocytopenia, aplastic anemia, and hemolytic anemia.
Cardiovascular: Orthostatic hypotension.
Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing anglitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions.
Other: Hyperglycemia, glucosuria, hyperurecemia, muscle spasm, weakness, restlessness, and tranaient blurred vision.
Fetal/Neonatal Morbidity and Mortlity: the use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contarctures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosis have also been reported, although it is not clear whether these occurrences where due to the ACE-inhibitor exposure.

DRUG INTERACTIONS
Diuretics:
Since captopril decreases aldosterone production, elevation of serum potassium may occur rarely, especially in patients with renal failure. Potassium sparing diuretics such as spironolactone, triametrene and amiloride if needed, should be used with caution since the may lead to significant increase of serum potassium.
Although most patients tolerate the antihypertensive effects of captopril well, those already on diuretic therapy may occasionally experience dizziness or lightheadedness, usually mild, indicative of hypotension that may occur within one hour of the first dose. In most instances, these symptoms are relieved simply by instructing the patient to lie down (see WARNINGS).
Other agents increasing serum potassium:
Potassium supplements should be given only for documented hypokalemia and then with caution, since the may lead to a significant increase in serum potassium. Salt substitute which contain potassium should also be used with caution.
Non-steroidal anti-inflammatory agents:
Concomitant therapy with indomethacin and possibly other non-steroidal anti-inflammatory agents may require an increase in the dose of captopril component.
Others:
Caution should be exercised in prescribing captopril for patients receiving concomitant therapy with immunosupresants, procainamide, allopurinol, and other drug known to cause neutropenia.

Thazides potentiate the action of ganglionic or peripheral adrenergic blocking drugs.
Thiazide drugs may increase the responsiveness to tubocurarine and may decrease arterial responsiveness to norepinephrine.
Drug/Laboratory Test Interactions:
Captopril may cause a false-positive urine test for acetone.

OVERDOSAGE:
In the event of over dosage, hypotension would be the most frequent and immediate problem. Volume expansion with an infusion of normal saline is the treatment of choice of normalization of the blood pressure. Captopril is removed by hemodialysis. The degree to which hdrochlorothiazide is removed by hemodilaysis has not been clearly established.

DOSAGE AND ADMINISTRATION
DOSAGE MUST BE INDIVIDULAIZED. SEE WARNINGS REGARDING HYPOTENSION IN SALT AND VOLUME DEPLETED PATIENTS.
In the treatment of hypertension CAPOZIDE may be used either as initial therapy or substitution therapy for patients receiving individual doses of captopril and a diuretic.
The combination tablet is not recommended for initial therapy in the treatment of heart failure.

Hypertension:
CAPOZIDE 50mg/25 mg once a day is the usual effective daily dose of CAPOZIDE.
CAPOZIDE 50mg/12.5 mg once a day has been shown to have beneficial effect5s in some patients and may be of value as initial therapy. If a satisfactory education of blood pressure has not been achieved after2-4 weeks of therapy with CAPOZIDE 25 mg/12.5 mg once daily, the dose m be increased to CAPOZIDE 50 mg/25 mg once a day. If a further increase in dose is needed, dosing should be increased to CAPOZIDE 50 mg/25 mg twice daily. The usual daily dose of captopril for the treatment of mild to moderate hypertension should not exceed 100 mg. in severe hypertension, where further blood pressure reduction is required, the dosage of CAPOZIDE 50 mg/25 mg twice daily may be supplemented b additional CAPOTEN (plain captopril tablets) to a maximum total daily dose of 450 mg captopril.

Heart failure:
Captopril has been used in conjunction with a diuretic and/or digitalis with the dosage of each individually titrated. The combination tablet (CAPOZIDE) should not be used to initiate therapy; however, once the optimal dose of captopril and diuretic has been established, CAPOZIDE may be substituted for continued therapy.

Patients with Renal Impairment:
Captopril excretion is reduced in the presence of impaired renal function. After the desired therapeutic effect has been achieved, the total daily dose of CAPOZIDE should be reduced or the dose interval increased (see PRECAUTIONS).

HOW SUPPLIED
Box of 3 strips x 10 tablets.

STORAGE
Store below 25° C.

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