Tablets

Moducren®

(timolol maleate, amiloride HCl, and hydrochlorothiazide)

MODUCREN® (hydrochlorothiazide, amiloride HCl, and timolol maleate) is an antihypertensive combining the active ingredients of MODURETIC® (hydrochlorothiazide and amiloride HCl) with BLOCADREN® (timolol maleate), products with complementary antihypertensive properties. Hydrochlorothiazide (a saluretic) and timolol maleate (a ß-adrenergic receptor blocking agent) are used singly and concomitantly for the treatment of hypertension. The antihypertensive effects of these agents are additive. Amiloride HCl provides potassium-conserving activity and when combined with hydrochlorothiazide, in MODURETIC, amiloride produces additive antihypertensive effects.

MODUCREN is a rational combination to be used for the treatment of patients with hypertension who may benefit from this type of therapy.

Amiloride when combined with hydrochlorothiazide has been shown to result in less excretion of magnesium than thiazide or loop diuretics used alone.

INDICATIONS

MODUCREN is indicated for the treatment of hypertension.

DOSAGE AND ADMINISTRATION

The recommended dosage is one to two tablets of MODUCREN 10 or one-half to one tablet of MODUCREN 20 administered on a once-a-day basis.

CONTRAINDICATIONS

-Bronchospasm (including bronchial asthma), or a history of bronchospasm, or severe chronic obstructive pulmonary disease.
-Sinus bradycardia
-Atrioventricular block
-Overt cardiac failure (see PRECAUTIONS)
-Cardiogenic shock
-Hyperkalemia (defined as >5.5 mEq/l)
-Other concomitant antikaliuretic therapy or potassium supplementation or potassium conserving agents (see PRECAUTIONS)
-Renal insufficiency (anuria, acute renal failure, severe progressive renal disease, and diabetic nephropathy (see also PRECAUTIONS)
-Hypersensitivity to any component of this product or other sulfonamide-derived drugs.
(See also USE IN PREGNANCY, NURSING MOTHERS, and PEDIATRIC USE under PRECAUTIONS)

PRECAUTIONS

Congestive Cardiac Failure

Sympathetic stimulation is essential for the support of the circulation in individuals with diminished myocardial contractility. In such patients, ß-adrenergic receptor blockade may be potentially dangerous by further depressing myocardial contractility and precipitating cardiac failure.

Thus, care is required before starting and during treatment with ß-adrenergic receptor blocking drugs in patients with cardiomegaly or a history of cardiac failure. Even in patients without a prior history of heart failure, the chronic use of ß-adrenergic receptor blocking agents may precipitate cardiac failure.

While the diuretic component of MODUCREN may reduce these hazards, they should nevertheless be considered. Some patients, especially those with manifest congestive cardiac failure, may require digitalization. If congestive cardiac failure persists, MODUCREN should be withdrawn.

Because of potential effects of ß-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow are observed, consideration should be given to discontinuing these agents.

Exacerbation of ischemic heart disease following abrupt withdrawal

Hypersensitivity to catecholamines has been observed in patients withdrawn from ß-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. Therefore, it is recommended that if MODUCREN is to be withdrawn, particularly in patients with ischemic heart disease, dosage should be gradually reduced.

Elective or emergency surgery

ß-adrenergic receptor blockade impairs the ability of the heart to respond to ß-adrenergically mediated reflex stimuli. Some patients receiving ß-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

For these reasons, in patients with angina pectoris undergoing elective surgery, some authorities recommend gradual withdrawal of ß-adrenergic receptor blocking agents.

If necessary, the effects of ß-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Renal and hepatic disease and electrolyte disturbances

MODUCREN should be used with caution in patients with renal (see CONTRAINDICATIONS) or hepatic disease and patients in whom fluid and electrolyte balance is critical.

When creatinine clearance falls below 30 ml/min thiazide diuretics are ineffective.

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of renal disease, the diuretic should be discontinued.

Metabolic or respiratory acidosis

Antikaliuretic therapy should be instituted only with caution in severely ill patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease or poorly controlled diabetes. When amiloride HCl is given to these patients, frequent monitoring of acid-base balance is necessary. Shifts in acid-base balance alter the ratio of extracellular to intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

Electrolyte and fluid balance status

As with any diuretic therapy, patients should be observed for clinical signs of fluid or electrolyte imbalance, particularly hyponatremia or hypochloremic alkalosis, hypokalemia and hypomagnesemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

The inclusion of amiloride HCl in the formulation of MODUCREN may diminish the likelihood of thiazide-induced hypochloremic alkalosis.

Likewise, any chloride deficit during thiazide therapy is generally mild and may be lessened by the amiloride HCl component of MODUCREN. Hypochloremia usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Amiloride HCl, a component of MODUCREN, has been shown to decrease the enhanced urinary excretion of magnesium which occurs when a thiazide or loop diuretic is used alone.

Hyperkalemia

Hyperkalemia (i.e., serum potassium levels over 5.5 mEq per liter) has been observed in patients who received amiloride HCl either alone or with other diuretics. This has been noted particularly in elderly patients, and in hospitalized patients with hepatic cirrhosis or cardiac edema who have known renal impairment, are seriously ill, or are receiving vigorous diuretic therapy. A few deaths have been reported in this group of patients in whom serum potassium was elevated. Such patients should be monitored carefully for clinical, laboratory, and electrocardiographic (ECG) evidence of hyperkalemia and for acidosis.

Treatment of Hyperkalemia: If hyperkalemia occurs in patients taking MODUCREN, the drug should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level.

Hypokalemia

Hypokalemia may develop during thiazide therapy, especially with brisk diuresis, when severe cirrhosis is present, during concomitant use of corticosteroids or ACTH, or after prolonged therapy. However, this usually is prevented by the amiloride HCl component of MODUCREN.

In severe and/or refractory cases of hypokalemia, if potassium supplementation in the form of medication or a potassium-rich diet is used, careful monitoring of the serum potassium level is necessary.

Diabetes mellitus, hypoglycemia

ß-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. Therefore, MODUCREN should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents.

To minimize the risk of hyperkalemia in diabetic or suspected diabetic patients the status of renal function should be known before initiating therapy with MODUCREN. Therapy should be discontinued for at least three days prior to glucose tolerance testing.

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Cutaneous and sensitivity reactions

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, and sclerosing serositis attributed to the ß-adrenergic receptor blocking agent, practolol. This syndrome has not been reported with timolol maleate or MODUCREN. A low incidence of rashes has occurred with therapy with timolol maleate and each of the other components of MODUCREN.

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Metabolic and endocrine

ß-adrenergic blockade may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of ß-blockade which might precipitate a thyroid storm.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

Musculoskeletal

ß-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness).

Pregnancy

Since MODUCREN has not been studied in human pregnancy, the drug is not recommended in pregnant patients. The use of any drug in women of childbearing potential requires that the anticipated benefit be weighed against possible hazards.

In patients receiving thiazides, these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing mothers

Timolol is detectable in human milk. It is not known whether amiloride HCl is excreted in human milk. However, thiazides appear in breast milk. Therefore, if use of MODUCREN is deemed essential, the patient should stop nursing.

Risk from anaphylactic reaction

While taking ß-Blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Pediatric use

The effect of therapy with MODUCREN in children has not been established. Therefore, MODUCREN is not recommended in the pediatric age group.

DRUG INTERACTIONS

MODUCREN may potentiate the action of other antihypertensive agents used concomitantly. Close observation of the patient is recommended when MODUCREN is administered to patients receiving catecholamine-depleting drugs such as reserpine or guanethidine because of the interaction of the ß-adrenergic receptor blocking component (timolol maleate) with these agents. Attenuation of the antihypertensive effect of ß-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs has been reported.

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and antihypertensive effects of diuretics.

Oral calcium antagonists may be used in combination with ß-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

The potential exists for hypotension, AV conduction disturbances, and left ventricular failure to occur in patients receiving a ß-blocking agent when an oral calcium entry blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a ß-blocker.

Intravenous calcium entry blockers should be used with caution in patients receiving ß-adrenergic blocking agents.

The concomitant use of ß-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

Potentiated systemic ß-Blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

ß-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, ß-adrenergic blocking agents should be withdrawn several days before the gradual withdraw of clonidine. If replacing clonidine by ß-blocker therapy, the introduction of ß-adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, cyclosporine or tacrolimus, the risk of hyperkalemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride HCl, may cause hyperkalemia and renal failure, particularly in elderly patients. Therefore, when amiloride HCl is used concomitantly with NSAIDs, renal function and serum potassium levels should be carefully monitored.

When given concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics - potentiation of orthostatic hypotension may occur.

Antidiabetic drugs - (oral agents and insulin) - dosage adjustment of the antidiabetic drug may be required.

Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - possible increased responsiveness to the muscle relaxant.

Lithium - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package inserts for lithium preparations before use of such preparations.

Drug/Laboratory Test Interactions - Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see PRECAUTIONS).

SIDE EFFECTS

MODUCREN is usually well tolerated and significant clinical adverse effects have been reported infrequently. The most common side effects experienced with MODUCREN are dizziness, asthenia, fatigue, and bradycardia. Clinical evaluation of MODUCREN has not revealed any adverse reactions peculiar to the combination. The adverse reactions that occurred were limited to those that have been reported previously for the individual components. The clinical adverse reactions are listed below:

Body as a Whole : Asthenia, Fatigue, Headache.
Cardiovascular : Bradycardia, Peripheral vascular disorder, (cold extremities), Hypotension, Syncope, Arrhythmia, Angina pectoris.
Respiratory : Dyspnea.
Digestive : Nausea, Dyspepsia, Vomiting, Gastrointestinal pain, Anorexia, Thirst.
Urogenital : Impotence.
Nervous : Dizziness, Vertigo, Paresthesia, Tremors.
Integumentary : Sweating.
Musculoskeletal : Muscle cramps.
Psychiatric : Insomnia, Nervousness, Depression, Somnolence, Abnormal dreaming, Sleep disturbance.
Other side effects have been reported with the individual components and may be considered potential side effects.

OVERDOSAGE

No data are available with regard to overdosage of MODUCREN in humans.

The acute toxicity in mice based on the LD_{50} of amiloride was slightly greater for a combination of hydrochlorothiazide-amiloride HCl-timolol maleate at a ratio of 4:10:1 than for amiloride given alone. This difference was not seen in similar studies done in male and female rats.

Little is known about the dialyzability of the individual components of MODUCREN. In a study of patients with renal failure, timolol did not dialyze readily.

No specific information is available on the treatment of overdosage with MODUCREN, and no specific antidote is available. Treatment is symptomatic and supportive. Therapy with MODUCREN should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage.

Hydrochlorothiazide-amiloride HCl : The signs and symptoms most likely to be expected with overdosage of hydrochlorothiazide and amiloride are dehydration and electrolyte imbalance. If hyperkalemia occurs, active measures should be taken to reduce the serum potassium levels.

Timolol maleate : The signs and symptoms most likely to be expected with overdosage of a ß-receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. The following therapeutic measures should be considered:

(1) *Gastric lavage.*
(2) *For symptomatic bradycardia*: Use atropine sulfate intravenously in a dosage of 0.25 – 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.
(3) *For hypotension:* Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases, the use of glucagon hydrochloride has been reported to be useful.
(4) *For bronchospasm:* Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.
(5) *For acute cardiac failure:* Conventional therapy with digitalis, diuretics, and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.
(6) *For heart block (second or third degree):* Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

AVAILABILITY

MODUCREN is available as tablets containing:

Timolol maleate	10 mg
Amiloride HCl	2.5 mg
Hydrochlorothiazide	25 mg

MODUCREN is supplied in boxes of 30, 100, and 1000 tablets.

KEEP MEDICAMENT OUT OF REACH OF CHILDREN.

Do not use after expiry date.

THIS IS A MEDICAMENT

-A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
-The doctor and the pharmacist are experts in medicine, its benefits and risks.
-Do not by yourself interrupt the period of treatment prescribed.
-Do not repeat the same prescription without consulting your doctor.

Storage Conditions : Store in a dry place below 30°C, protected from light. Do not refrigerate.

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ALGORITHM S.A.L.
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