PRODUCT MONOGRAPH

PrTEVA-TRIAMTERENE/HCTZ

(Triamterene 50 mg and Hydrochlorothiazide 25 mg)

Diuretic/Antihypertensive

Teva Standard

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NAME OF DRUG

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(Triamterene 50 mg and Hydrochlorothiazide 25 mg)

THERAPEUTIC CLASSIFICATION

Diuretic/Antihypertensive

ACTION

TEVA-TRIAMTERENE/HCTZ (triamterene and hydrochlorothiazide) is a combination of two diuretics with different but complimentary modes of action. The natriuretic, diuretic and antihypertensive activity of the thiazide is supplemented by the mild diuretic and potassium-conserving action of triamterene. The combination reduces the risk of hypo-kalemia and of acid-base imbalance seen sometimes with the use of hydrochlorothiazide alone.

The onset of the diuretic action of TEVA-TRIAMTERENE/HCTZ is within 1 hour, reaches a peak at 2 to 3 hours and tapers off during the subsequent 7 to 9 hours.

Hydrochlorothiazide is a diuretic and antihypertensive agent. It affects the renal tubular mechanism of electrolyte reabsorption.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts, and may cause a simultaneous, usually minimal, loss of bicarbonate. Natriuresis is usually accompanied by loss of potassium.

Triamterene inhibits the reabsorption of sodium ions in exchange for potassium and hydrogen ions at that segment of the distal tubule under the control of adrenal mineralo-corticoids. Triamterene acts directly on tubular transport and is independent of aldosterone. By inhibiting the ion exchange mechanism of the distal tubule, triamterene reduces the excess loss of potassium, hydrogen and chloride ions induced by hydrochlorothiazide. Triamterene alone has little or no antihypertensive effect.

INDICATIONS

Fixed-dose combination drugs are not indicated for initial therapy. Patients should be titrated on the individual drugs. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. If during maintenance therapy dosage adjustment is necessary it is advisable to use the individual drug's.

TEVA-TRIAMTERENE/HCTZ (triamterene and hydrochlorothiazide) is indicated in the maintenance therapy of:

Patients with edema associated with congestive heart failure, hepatic cirrhosis, and nephrotic syndrome; also in steroid-induced edema and idiopathic edema.

Patients with mild to moderate hypertension in those patients who have developed hypokalemia while on thiazide-like diuretics alone, and in those patients in whom potassium depletion is considered especially dangerous (e.g. digitalized patients). Medical opinion is not unanimous regarding the incidence and/or clinical significance of hypokalemia occurring among hypertensive patients treated with thiazide-like diuretics alone, and concerning the use of potassium-sparing combinations as routine therapy in hypertension.

CONTRAINDICATIONS

TEVA-TRIAMTERENE/HCTZ should not be used in patients with pre-existing elevated serum potassium, or in patients who develop hyperkalemia while on the drug.

TEVA-TRIAMTERENE/HCTZ is contraindicated in patients with anuria, severe or progressive renal dysfunction, including oliguria and progressively increasing azotemia.

Severe or progressive hepatic dysfunction contraindicates further use of TEVA-TRIAMTERENE/HCTZ.

TEVA-TRIAMTERENE/HCTZ is contraindicated in patients who are hypersensitive to triamterene, hydrochlorothiazide, or other sulfonamide-derived drugs.

WARNINGS

Potassium supplementation in the form of medication should not be used routinely in conjunction with TEVA-TRIAMTERENE/HCTZ since hyperkalemia may result. Abnormal elevation of serum potassium, although uncommon, is potentially the most serious electrolyte

disturbance. Hyperkalemia has been reported (overall incidence less than 8%) and in some cases has been associated with cardiac irregularities. Hyperkalemia is more likely to occur in patients who are seriously ill, have known renal impairment, or in elderly (incidence approximately 12%) or diabetic patients with confirmed or suspected renal insufficiency. Fatalities have been reported in such patients. All patients on TEVA-TRIAMTERENE/HCTZ should be monitored carefully for clinical laboratory and electrocardiographic evidence of hyperkalemia and for acidosis.

Combination therapy with other potassium-conserving agents is potentially hazardous, since both can cause potassium retention and, in some cases, hyperkalemia. Such combination therapy should not be used routinely. If it is deemed essential the patient must be under close supervision and serum potassium levels determined frequently.

Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities.

When abnormal, the ECG in hyperkalemia is characterized primarily by tall, peaked T waves or elevations from previous tracings. There may also be lowering of the R wave and increased depth of the S wave, widening or disappearance of the P wave, progressive widening of the QRS complex, prolongation of the PR interval, and ST depression.

If hyperkalemia develops, discontinue TEVA-TRIAMTERENE/HCTZ, substitute the thiazide alone and restrict dietary potassium intake. When indicated by the clinical situation, excess potassium may be removed by dialysis or oral or rectal administration of sodium polystyrene sulfonate. Infusion of glucose and insulin have also been used to treat hyperkalemia.

TEVA-TRIAMTERENE/HCTZ should 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.

Since triamterene has been found in renal stones, this should be taken into consideration before TEVA-TRIAMTERENE/HCTZ is administered to patients who have a history of renal stones.

Usage in Pregnancy:

Thiazides cross the placental barrier and appear in cord blood. Triamterene has been shown to do the same in ewes and this may occur in, humans. The use of TEVA-TRIAMTERENE/HCTZ in women who are or may become pregnant requires that the anticipated benefits be weighed against possible risks to the fetus. Hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

Usage in Nursing Mothers:

Thiazides appear in breast milk and triamterene appears in cow's milk. TEVA-TRIAMTERENE/HCTZ should be discontinued or the patient should stop nursing.

Usage in Children:

The safety for use of TEVA-TRIAMTERENE/HCTZ in children has not been established,

PRECAUTIONS

Careful checks should be kept for signs of fluid or electrolyte imbalance (hyperkalemia, hyponatremia, hypokalemia and hypochloremic alkalosis). Serum and urine electrolyte

determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Because of the potassium-sparing characteristic of triamterene, hypokalemia occurs less frequently with TEVA-TRIAMTERENE/HCTZ than with thiazides alone. The effects of digitalis on the heart may be exaggerated in patients with hypokalemia and sighs of digitalis intoxication may be seen at doses previously tolerated.

Triamterene may cause a decreasing alkali reserve with the possibility of metabolic acidosis.

Thiazides can precipitate hepatic coma in patients with severe liver disease. Potassium depletion induced by the thiazide may be important in this connection. Administer TEVA-TRIAMTERENE/HCTZ cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor; if mental confusion increases discontinue TEVA-TRIAMTERENE/HCTZ for a few days. Attention must be given to other factors that may precipitate hepatic coma, such as blood in the gastrointestinal tract or pre-existing potassium depletion.

Any chloride deficit is-generally mild and usually does not require specific treatment. A chloride deficit may be corrected by the use of ammonium chloride (except in patients with hepatic disease) and largely prevented by a near normal salt intake.

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.

Increases in urea nitrogen level and/or creatinine level have been reported. This apparently is secondary to a reversible reduction of glomerular filtration rate or a depletion of intravascular fluid volume (prerenal azotemia). Levels usually return to normal when TEVA-TRIAMTERENE/HCTZ is discontinued. Careful monitoring of BUN or serum creatinine levels is important when administering TEVA-TRIAMTERENE/HCTZ. If azotemia increases discontinue TEVA-TRIAMTERENE/HCTZ (see Contraindications).

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands .with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

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

Thiazides may cause hyperglycemia and glycosuria and may alter insulin requirements in diabetics.

Patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions. There have been reports of blood dyscrasias in patients receiving triamterene. Leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Cirrhotics with splenomegaly may have marked variations in their blood pictures - including thrombocyte and leukocyte levels – which are not related to drug therapy. Since the triamterene component of TEVA-TRIAMTERENE/HCTZ is a weak folic acid antagonist, it may contribute to the appearance of megaloblastosis in cases where folic acid stores are depleted. Periodic blood studies in these patients are recommended.

Sensitivity reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

The possibility of exacerbation or activation of systemic lupus erythmatosus have been reported.

Hydrochlorothiazide, decreases arterial responsiveness to norepinephrine. This dimunition is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

The antihypertensive effect of TEVA-TRIAMTERENE/HCTZ may be enhanced in the post-sympathectomy patient.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics.

Thiazide drugs may increase the responsiveness to tubocurarine.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity.

ADVERSE REACTIONS

The following adverse reactions have been associated with the use of thiazide diuretics and/or triamterene:

Gastrointestinal: Dry mouth, anorexia, gastric irritation, nausea, vomiting, cramps, diarrhea, constipation, jaundice (intrahepatic cholestatic), pancreatitis, sialadenitis.

Note: Symptoms of nausea and vomiting can also indicate electrolyte imbalance. (see Precautions).

Central Nervous System: Dizziness, vertigo, paresthesias, headache, xanthopsia.

Dermatologic - Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions.

Hematologic: Leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

Cardiovascular: Orthostatic hypotension.

Renal: Triamterene (and its metabolite p-hydroxytriamterene) have been found in renal stones in association with the usual components. Rare cases of interstitial nephritis have been reported.

Electrolyte Imbalance: (See Warnings and Precautions).

Miscellaneous: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Newborn, whose mothers had received thiazides during pregnancy, in rare instances have developed thrombocytopenia or pancreatitis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Electrolyte imbalance is the major concern (See Warnings section). Symptoms reported include: polyuria, nausea, vomiting, weakness, lassitude, fever, flushed face, and hyperactive deep tendon reflexes. If hypotension occurs, it may be treated with pressor, agents such as levarterenol to maintain blood pressure. Carefully evaluate the electrolyte pattern and fluid balance. Induce immediate evacuation of the stomach through emesis or gastric lavage. There is no specific antidote.

DOSAGE AND ADMINISTRATION

Dosage must be determined for individual patients by titration of each component separately. Where the fixed combination in TEVA-TRIAMTERENE/HCTZ provides the dosage so determined, TEVA-TRIAMTERENE/HCTZ may be used for maintenance therapy. If during maintenance therapy dosage adjustment is necessary, it is advisable to use the individual drugs.

TEVA-TRIAMTERENE/HCTZ should be taken after an adequate meal,

Adult dosage:

Edema: The usual dosage is one tablet twice daily after meals. When dry weight is reached, one tablet daily will usually suffice. In some patients, one tablet every other day may be indicated.

Hypertension: The usual dosage is one tablet twice daily after meals. Dosage may be increased or decreased according to patient's need. If two or more tablets per day are needed they should be given in divided doses. Maximum daily dosage should not exceed four tablets (200 mg

triamterene and 100 mg hydrochlorothiazide), and at this dosage the incidence of adverse effects may increase.

AVAILABILITY

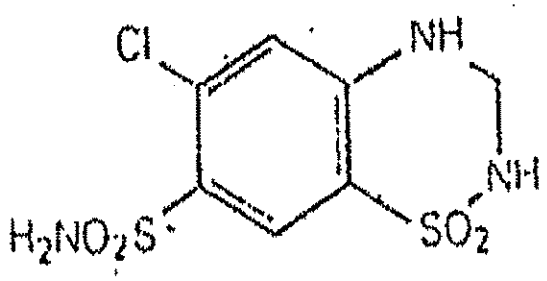
TEVA-TRIAMTERENE/HCTZ:

Each peach coloured round, flat-faced bevel-edged compressed tablet, engraved novo on one side and $\frac{25}{50}$ on the reverse contains: Triamterene 50.0 mg and Hydrochlorothiazide 25.0 mg.

Bottles of 100 and 1000. Unit Dose Strips of 100.

CHEMISTRY

Hydrochlorothiazide:

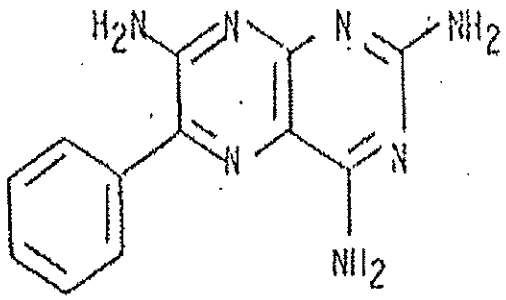


Molecular Formula: $C_7H_8ClN_3O_4S_2$ Molecular Weight: 297.73

Chemical Name: 6-chloro-3,4-dihydro-2H-l,2, 4-benzothiadiazine7-sulfonamide 1, 1-dioxide.

Description: A white, or practically white, practically odourless, crystalline powder, slightly soluble in water.

Triamterene:



Molecular Formula: $C_{12}H_{11}N_7$ Molecular Weight: 253.27

Chemical Name: 2,4,7-triamino-6-phenylpteridine.

Description: A yellow, odourless, crystalline powder; practically insoluble in water, chloroform or ether.

PHARMACOLOGY

Hydrochlorothiazide is a diuretic and antihypertensive agent. It inhibits the reabsorption of sodium and chloride in the distal segment and causes a simultaneous usually minimal loss of bicarbonate. Hydrochlorothiazide decreases the renal excretion of calcium, presumably by a direct action on renal transport. Magnesium excretion is increased.

Hydrochlorothiazide is absorbed from the gastrointestinal tract relatively rapidly since a demonstrable diuretic effect is seen within one hour and reaches a peak effect in about 4 hours. Its action persists for approximately 6-12 hours. Hydrochlorothiazide is eliminated rapidly by the kidney.

Triamterene has no significant pharmacological actions other than those on the kidney.

Triamterene inhibits the reabsorption of sodium ions in exchange for potassium arid hydrogen ions in the distal renal tubule through a direct effect and not by competitive aldosterone antagonism. The degree of natriuresis and diuresis produced by triamterene alone is limited; it has an additive diuretic effect when used with a thiazide diuretic.

Triamterene is rapidly absorbed from the gastrointestinal tract but to a variable extent (30 - 70% of the oral dose). It is excreted in the urine with a peak in renal excretion within 1 to 2 hours after oral ingestion. Diuretic effect following a single dose is evident within 2-4 hours and tapers off 7-9 hours after administration.

The peak plasma concentration of triamterene is reached 2 to 4 hours after an oral dose and the half-life of the drug in plasma ranges from 1.5 to 2 hours. Approximately 50% of triamterene is bound to human plasma protein.

Triamterene and its metabolites are excreted by the kidney by filtration and tubular secretion. The peak in triamterene renal excretion occurs 1 to 2 hours after dosing. About 20% of an oral dose appears unchanged in the urine, 70% as the sulfate ester of hydroxytriamterene and 10% as free hydroxytriamterene and triamterene glucuronide. Hydroxytriamterene has diuretic activity.

TOXICOLOGY

Hydrochlorothiazide:

In mice, the oral and i.v. LD_{50}s were greater than 10,000 mg/kg and 884 mg/kg respectively. In rats, the oral and i.p. LD_{50}s were greater than 10,000 mg/kg and 3,130 mg/kg respectively.

Reported results of a six month chronic oral toxicity study in the rat using doses of up to 2 g/kg/day (5 days/week) showed no signs of toxicity.

In dogs, oral doses up to 500 mg/kg/day were given 7 days per week for periods as long as 45 weeks. Slight depression of plasma potassium and small amounts of yellow crystalline precipitate in the bladder in two of twelve dogs were found on gross examination. Histomorphologic examination showed no drug related changes.

Reproductive studies in rats and mice and a teratology study in rabbits showed no evidence of effects due to drug administration.

Triamterene:

The oral LD_{50} values for triamterene were found to be:

Mouse: 840 mg/kg (95% C.L. 794 to 959 mg/kg)

Rat: 3.59 g/kg (95% C.L. 2.80 g to 4.60 g/kg).

Groups of 4 to 6 dogs were orally administered a 1:1 combination of triamterene and hydrochlorothiazide at dose levels of 0, 2, 4 and 15 mg/kg/day of each component for 15 weeks. Elevations of serum alkaline phosphatase of borderline significance and sharp increases in SGPT were seen in the high dose group at 10 weeks with a return to normal at 15 weeks[13].

Groups of rats were orally administered triamterene-hydrochlorothiazide (1:1) in increasing doses to a maximum of 500 mg/kg/day (each ingredient) for 27 days. Male rats and the surviving female rats (5 of 10) at the maximum dose had enlarged kidneys and a characteristic nephropathy varying from slight to severe[13].

Dogs administered 50 mg/kg/day (each ingredient) triamterene-hydrochlorothiazide (1:1) for 6 days exhibited anorexia, bloody diarrhea mixed with mucous and granular yellow material in the feces. When the dose was increased to 200 mg/kg/day (each component) three of six dogs had elevated SGPT and four of six had slightly elevated serum alkaline phosphatase on day 12, and on day 25 exhibited dyspnea, mild convulsions, prostration and death. Drug-related toxic nephropathy was clearly demonstrated[13].

Reproductive Study:

A reproductive study in 3 groups of 40 male and female rats given a 2:1 combination of triamterene and hydrochlorothiazide in food for 60 days prior to mating and through two litters

was performed. One group was a control, the second received 9 mg/kg/day of the combination and a third group was started on 30 mg/kg/day, but because of weight loss this was lowered to 15 mg/kg/day on day 5 and on day 52 to 12 mg/kg/day and kept there throughout the study. Mortality among the parent rats was limited to 1 low dose female who died of dystocia. In the first breeding period the live birth index and viability index were similar in all 3 groups. Litter size, birth weight and mean weight of progeny at 3 weeks of age did not differ significantly. Similar results were found in the second breeding period although 3 congenital anomalies (hydrops) were noted, one in each of the 3 groups[13].

Teratology Study:

Maass et al administered triamterene in doses ranging from 11.1 to 32.0 mg/kg/day to 4 groups of 15 female rats on the 8th through l0th day of gestation to investigate its effect on maternal weight gain, litter size and live birth index. Adverse effects on fetal tissue could not be demonstrated nor were physical abnormalities observed in the progeny[10].

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