PRODUCT MONOGRAPH

[Pr] PRO-TRIAZIDE

(Triamterene 50 mg and Hydrochlorothiazide 25 mg)

Diuretic/Antihypertensive

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Control No. 175672

NAME OF DRUG

[Pr] PRO-TRIAZIDE

(Triamterene 50 mg and Hydrochlorothiazide 25 mg)

THERAPEUTIC CLASSIFICATION

Diuretic/Antihypertensive

ACTION

Pro-Triazide (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 hypokalemia and of acid-base imbalance seen sometimes with the use of hydrochlorothiazide alone.

A single dose comparative oral bioavailability study of PRO-TRIAZIDE and Dyazide tablets was performed on 18 normal male volunteers. The dose administered was two tablets, that is 100 mg triamterene and 50 mg hydrochlorothiazide. The results can be summarized as follows:

Triamterene

	Pro-Triazide	Dyazide
AUC_{0-24} hrs (ng•hrs/mL)	476	474
C_{max} (ng/mL)	143	140
T_{max} (hrs)	0.9	1.1
$T_{1/2}$ (hrs)	4.9	4.9

Hydrochlorothiazide

	Pro-Triazide	Dyazide
AUC_{0-24} hrs (ng•hrs/mL)	1708	1736
C_{max} (ng/mL)	283	276
T_{max} (hrs)	2.1	2.1
$T_{1/2}$ (hrs)	6.0	6.0

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 mineralocorticoids. 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 drugs.

PRO-TRIAZIDE (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 steroidinduced 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

PRO-TRIAZIDE should not be used in patients with pre-existing elevated serum potassium, or in patients who develop hyperkalemia while on the drug.

PRO-TRIAZIDE 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 Pro-Triazide.

PRO-TRIAZIDE 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 PRO-TRIAZIDE 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 PRO-TRIAZIDE 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 Pro-Triazide, 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.

PRO-TRIAZIDE 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 PRO-TRIAZIDE *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 PRO-TRIAZIDE 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. PRO-TRIAZIDE should be discontinued or the patient should stop nursing.

Usage in Children:
The safety for use of PRO-TRIAZIDE in children has not been established.

Ophthalmologic:

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

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 PRO-TRIAZIDE than with thiazides alone. The effects of digitalis on the heart may be exaggerated *in* patients with hypokalemia and signs 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 PRO-TRIAZIDE cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor: if mental confusion increases discontinue PRO-TRIAZIDE 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 PRO-TRIAZIDE is discontinued. Careful monitoring of BUN or serum creatinine levels is important when administering Pro-Triazide. If azotemia increases discontinue PRO-TRIAZIDE (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 PRO-TRIAZIDE 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.

The antihypertensive effect of PRO-TRIAZIDE may be enhanced in the post-sympathectomy patient.

DRUG INTERACTIONS

Drug-Drug Interactions:

Proper Name	Ref.	Effect	Clinical comment
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics	Monitor serum potassium level.
Antidiabetic agents (e.g. insulin and oral hypoglycemic agents)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACEI, ARB, and direct renin inhibitors).	
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, e.g. cholestyramine	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothaizide by 30-35%.	Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.

Proper Name	Ref.	Effect	Clinical comment
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur.	Monitor serum potassium, and adjust medications, as required.
Digoxin	CT	Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazide, as required.
Drugs that alter GI motility, i.e., anti-cholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RC	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of gout medications may be required.
Lithium	CT	Thiazide diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of thiazide diuretics with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely.
Nonsteroidal anti-inflammatory drugs (NSAID)	CT	NSAID-related retention of sodium and water antagonises the diuretic and antihypertensive effects of thiazides. NSAID-induced inhibition of renal prostaglandins leading to decreases of renal blood flow, along with thiazide-induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required.

Proper Name	Ref.	Effect	Clinical comment
Selective serotonin reuptake inhibitors (SSRIs, e.g. citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, e.g., tubocurare	C	Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants, such as curare derivatives	
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels. Use potassium supplements, or adjust topiramate dose as necessary.

Legend: C = Case Study; RCS = Retrospective Cohort Study; CT = Clinical Trial; T = Theoretical

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

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

PRO-TRIAZIDE 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.

DOSAGE FORMS, COMPOSITIONS AND PACKAGING

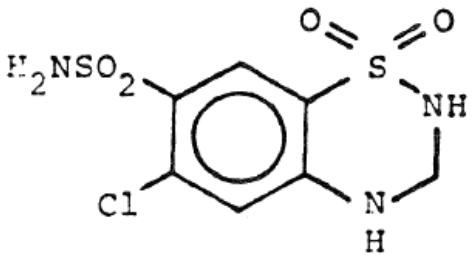
Each round, flat-faced, single-scored, yellow PRO-TRIAZIDE tablet contains: triamterene 50 mg and hydrochlorothiazide 25 mg.

In addition to the active ingredients, triamterene and hydrochlorothiazide, each tablet also contains the non-medicinal ingredients colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, and sunset yellow aluminium lake 40 %.

Bottles of 100, 1000, and 5000 tablets.

CHEMISTRY

Hydrochlorothiazide



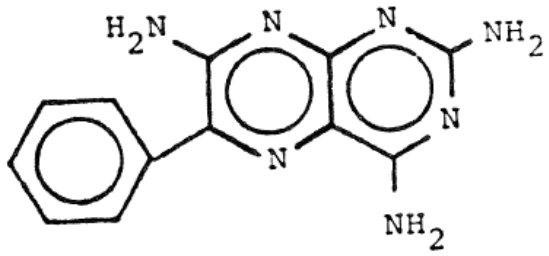
Molecular Formula: $C_7H_8ClN_3O_4S_2$

Molecular Weight: 297.72 g/mol

Chemical Name: 6-Chloro-3,4-dihydro-2H-l,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Description: A white or almost white crystalline compound with a slightly bitter taste, almost insoluble in water.

Triamterene



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

Molecular Weight: 253.3 g/mol

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

Description: A yellow odourless crystalline compound, tasteless at first with a slightly bitter aftertaste; practically insoluble in water, or chloroform; unstable to light.

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 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 action other than those on the kidney.

Triamterene inhibits the reabsorption of sodium ions in exchange for potassium and hydrogen ions in the distal renal tubule through a direct effect and not by competitive aldosterone antagonism. The degree of natriuresis and dieresis 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 sulphate ester of hydroxytriamterene and 10% as free hydroxytriamterene and triamterene glucuronide. Hydroxytriamterene has diuretic activity.

TOXICOLOGY

Hydrochlorothiazide:

In rats, the oral LD50's were greater than 2750 mg/kg.

Triamterene:

The oral LD50 values for triamterene were found to be:

Mouse: 490 mg/kg (95% C.L. 398 to 603 mg/kg)

Rat: 1600 mg/kg (95% C.L. 1409 to 1817 mg/kg)

Combination: Triamterene and Hydrochlorothiazide

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.

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.

Dogs administered 50 mg/kg/day (each ingredient) triarnterenehydrochlorothiazide (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 nephropatpy was clearly demonstrated.

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.

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 8^{th} through 10^{th} 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.

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PART III: CONSUMER INFORMATION

[Pr]PRO-TRIAZIDE
(Triamterene 50 mg and Hydrochlorothiazide 25 mg Tablets)

Read this carefully before you start taking PRO-TRIAZIDE and each time you get a refill. This leaflet is a summary and will not tell you everything about PRO-TRIAZIDE. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about PRO-TRIAZIDE.

ABOUT THIS MEDICATION

What the medication is used for:
PRO-TRIAZIDE is used in adults for:
- Swelling due to:
  - steroid use
  - heart, liver or kidney problems
  - other unknown causes
- High blood pressure (also called hypertension)

What it does:
PRO-TRIAZIDE contains a combination of 2 drugs, triamterene and hydrochlorothiazide:
- Triamterene helps the body lose excess salt but keep a normal amount of potassium (an electrolyte) in the blood.
- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. This lowers blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking PRO-TRIAZIDE regularly even if you feel fine.

When it should not be used:
Do not take PRO-TRIAZIDE if you:
- Are allergic to triamterene and hydrochlorothiazide, or to any non-medicinal ingredient in the formulation.
- Are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in **"-MIDE"**.
- Have difficulty urinating or produce no urine.
- Have severe or worsening kidney or liver problems.
- Are breastfeeding. PRO-TRIAZIDE passes into breast milk.
- Have high potassium levels (hyperkalemia).
- Have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

Because lactose is a non-medicinal ingredient in PRO-TRIAZIDE.

What the medicinal ingredients are:
Triamterene and hydrochlorothiazide.

What the non-medicinal ingredients are:
Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, and sunset yellow aluminium lake 40 %

What dosage forms it comes in:
Tablet; triamterene 50 mg and hydrochlorothiazide 25 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use PRO-TRIAZIDE talk to your doctor, nurse, or pharmacist if you:
- Are allergic to penicillin.
- Have diabetes, liver or kidney disease.
- Have a history of kidney stones.
- Have lupus or gout.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are using any form of potassium supplementation.
- Are taking any other potassium-conserving medications or "water pills".
- Are pregnant or thinking of becoming pregnant.
- Are less than 18 or over 65 years ~~old~~ of age.

Hydrochlorothiazide in PRO-TRIAZIDE can cause Sudden Eye Disorders:
- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

These eye disorders are related and can develop within hours to weeks of starting PRO-TRIAZIDE.

You may become sensitive to the sun while taking PRO-TRIAZIDE. Exposure to sunlight should be minimized until you know how you respond.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to PRO-TRIAZIDE. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with PRO-TRIAZIDE:
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amphotericin B, an antifungal drug.
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Digoxin, a heart medication.
- Drugs that slow down or speed up bowel function, including atropine, metoclopramide, and domperidone.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Gout medications, including allopurinol and probenecid.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.

- Other blood pressure lowering drugs. When taken in combination with PRO-TRIAZIDE, they may cause excessively low blood pressure.
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurare.

PROPER USE OF THIS MEDICATION

Take PRO-TRIAZIDE exactly as prescribed. It is recommended to take your dose at about the same time every day.

PRO-TRIAZIDE should be taken after a meal.

Usual Adult dose:
Patients should be individually titrated for each component separately.

For Edema: usually 1 tablet twice daily. In some patients, one tablet every day or every other day may be indicated.

For Hypertension: usually 1 tablet twice daily, dosage may be increased or decreased according to patient's need. Maximum daily dose should not exceed 4 tablets.

Do not adjust your dosage by yourself. Please consult your doctor and follow the given advice.

Overdose:

If you think you have taken too much PRO-TRIAZIDE contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- muscle cramps, spasms, and pain, weakness, restlessness
- dizziness, pins and needles in your fingers, headache
- constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth, dry mouth
- reduced libido
- bleeding under the skin, rash, red patches on the skin

If any of these affects you severely, tell your doctor, nurse or pharmacist.

PRO-TRIAZIDE can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up.	√		
	Decreased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		√	
Uncommon	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
	Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor, nurse, or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Increased blood sugar: frequent urination, thirst, and hunger	√		
	Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
Rare	**Decreased Platelets:** bruising, bleeding, fatigue and weakness		√	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
Very rare	**Toxic Epidermal Necrolysis:** severe skin peeling, especially in mouth and eyes			√
Unknown	**Eye Disorders:** **- Myopia:** sudden near sightedness or blurred vision **- Glaucoma:** increased pressure in your eyes, eye pain			√
	Anemia: fatigue, loss of energy, weakness, shortness of breath.		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor, nurse, or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
	Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		√	

This is not a complete list of side effects. For any unexpected effects while taking PRO-TRIAZIDE, contact your doctor, nurse, or pharmacist.

HOW TO STORE IT

Store at room temperature, 15-30°C (59-86°F).

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or info@prodoc.qc.ca.

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