Product Monograph

Including Patient Medication Information

[Pr]APO-TRIAZIDE

Triamterene and Hydrochlorothiazide Tablets

For Oral use

50 mg Triamterene and 25 mg Hydrochlorothiazide

Apotex Standard

Diuretic/Antihypertensive

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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Recent Major Label Changes

4. Dosage and Administration, 4.2. Recommended Dose and Dosage Adjustment	2026-08
7. Warnings and Precautions, Ophthalmologic	2026-08
7. Warnings and Precautions, Respiratory	2026-08

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent Major Label Changes 2

Table of Contents 2

Part 1: Healthcare Professional Information 5

1. Indications 5

1.1. Pediatrics 5

1.2. Geriatrics 5

2. Contraindications 5

3. Serious Warnings and Precautions Box 6

4. Dosage and Administration 6

4.1. Dosing Considerations 6

4.2. Recommended Dose and Dosage Adjustment 6

4.4. Administration 6

4.5. Missed Dose 7

5. Overdose 7

6. Dosage Forms, Strengths, Composition, and Packaging 7

7. Warnings and Precautions 7

General 8

Carcinogenesis and Mutagenesis 8

Driving and Operating Machinery 8

Endocrine and Metabolism 8

Hematologic 10

Hepatic/Biliary/Pancreatic 10
Immune 10
Ophthalmologic 10
Perioperative Considerations 11
Renal 11
Respiratory 11
Sensitivity/Resistance 11
Skin 12
7.1. Special Populations 12
7.1.1. Pregnancy 12
7.1.2. Breastfeeding 12
7.1.3. Pediatrics 12
7.1.4. Geriatrics 12
8. Adverse Reactions 12
8.1. Adverse Reaction Overview 12
8.2. Clinical Trial Adverse Reactions 12
8.5. Post-Market Adverse Reactions 13
9. Drug Interactions 14
9.4. Drug-Drug Interactions 14
9.5. Drug-Food Interactions 17
9.6. Drug-Herb Interactions 17
9.7. Drug-Laboratory Test Interactions 17
10. Clinical Pharmacology 17
10.1. Mechanism of Action 17
10.2. Pharmacodynamics 18
10.3. Pharmacokinetics 18
11. Storage, Stability, and Disposal 19
Part 2: Scientific Information 20
13. Pharmaceutical Information 20
14. Clinical Trials 21
14.2. Comparative Bioavailability Studies 21

15. Microbiology 21

16. Non-Clinical Toxicology.....21

Patient Medication Information.....24

Part 1: Healthcare Professional Information

1. Indications

APO-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 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.

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.

1.1. Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of APO-TRIAZIDE in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3. Pediatrics).

1.2. Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 3. Serious Warnings and Precautions Box).

2. Contraindications

APO-TRIAZIDE is contraindicated in:

- Patients with pre-existing elevated serum potassium, or in patients who develop hyperkalemia while on the drug.
- Patients with anuria, severe or progressive renal dysfunction, including oliguria and progressively increasing azotemia.

- Patients with severe or progressive hepatic dysfunction as it contraindicates further use of APO-TRIAZIDE.
- Patients who are hypersensitive to triamterene, hydrochlorothiazide, or other sulfonamide-derived drugs (see 6. Dosage Forms, Strengths, Composition, and Packaging).

3. Serious Warnings and Precautions Box

- Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities (see 7. Warnings and Precautions, Hyperkalemia).

4. Dosage and Administration

4.1. Dosing Considerations

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

4.2. Recommended Dose and Dosage Adjustment

- **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.

- **Drug discontinuation**

If a diagnosis of acute respiratory distress syndrome (ARDS) is suspected, APO-TRIAZIDE should be withdrawn and the appropriate treatment given.

4.4. Administration

- Take APO-TRIAZIDE exactly as prescribed. It is recommended to take your dose at about

the same time every day.
- APO-TRIAZIDE should be taken after an adequate meal.

4.5. Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule.

5. Overdose

Electrolyte imbalance is the major concern (see 7. Warnings and Precautions, Endocrine and Metabolism 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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Oral	Tablet; 50 mg of Triamterene and 25 mg of Hydrochlorothiazide	colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate and sunset yellow aluminium lake 40 %.

Description

Each light orange, round, flat-faced, bevelled edge tablet, scored and engraved with "APO" over "50-25" on one side, other side plain, contains: 50 mg triamterene and 25 mg hydrochlorothiazide.

Bottles of 100, 1000, and 5000 tablets.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

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

Carcinogenesis and Mutagenesis

Non-melanoma skin cancer: An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use (see 8. Adverse Reactions, 8.5. Post-Market Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16. Non-Clinical Toxicology, Carcinogenicity, Hydrochlorothiazide).

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones, and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate protection (e.g. a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g., light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see 8. Adverse Reactions, 8.5. Post-Market Adverse Reactions).

Driving and Operating Machinery

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

Endocrine and Metabolism

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 APO-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.

Hyperkalemia: 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 APO-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.

Electrolyte Imbalance and BUN Increases: 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.

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.

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 APO-TRIAZIDE is discontinued. Careful monitoring of BUN or serum creatinine levels is important when administering APO-TRIAZIDE. If azotemia increases discontinue APO-TRIAZIDE (see 2. Contraindications).

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

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

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.

Hematologic

Patients should be observed regularly for the possible occurrence of blood dyscrasias, 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.

Hepatic/Biliary/Pancreatic

Patients should be observed regularly for the possible occurrence of liver damage.

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 APO-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.

APO-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.

Thiazides can precipitate hepatic coma in patients with severe liver disease. Potassium depletion induced by the thiazide may be important in this connection. Administer APO-TRIAZIDE cautiously and be alert for such early signs of impending coma as confusion, drowsiness and tremor: if mental confusion increases discontinue APO-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.

Immune

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

Ophthalmologic

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma related to Hydrochlorothiazide: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision 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 sulfonamide or penicillin allergy.

Perioperative Considerations

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

Renal

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

Respiratory

Acute Respiratory Toxicity: Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary edema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnea, fever, pulmonary deterioration and hypotension. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Sensitivity/Resistance

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

Skin

Photosensitivity: Photosensitivity reactions have been reported with the use of thiazide diuretics. If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

7.1. Special Populations

7.1.1. 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 APO-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.

7.1.2. Breastfeeding

Thiazides appear in breast milk and triamterene appears in cow's milk. APO-TRIAZIDE should be discontinued or the patient should stop nursing.

7.1.3. Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of APO-TRIAZIDE in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (See 3 Serious Warnings and Precautions Box).

8. Adverse Reactions

8.1. Adverse Reaction Overview

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 APO-TRIAZIDE should be monitored carefully for clinical laboratory and electrocardiographic evidence of hyperkalemia and for acidosis.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

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

Cardiovascular: Orthostatic hypotension.

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.

Electrolyte Imbalance: (See 7. Warnings and Precautions, Endocrine and Metabolism).

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.

Hematologic: Leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia.

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.

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.

8.5. Post-Market Adverse Reactions

Acute respiratory distress syndrome (ARDS) (very rare)

Eye disorders – choroidal effusion, acute myopia, acute angle-closure glaucoma (frequency unknown).

Non-melanoma skin cancer

Some pharmacoepidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis undertaken by Health Canada suggested that, with important uncertainty, the use of hydrochlorothiazide for several years (>3 years) could lead to:

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);
- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

9. Drug Interactions

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 – Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	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).	

Proper/ Common name	Source of Evidence	Effect	Clinical comment
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 hydrochlorothiazide 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.
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,	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely.

Proper/ Common name	Source of Evidence	Effect	Clinical comment
		which may lead to fatal arrhythmic events.	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, RCS	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	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required.

Proper/ Common name	Source of Evidence	Effect	Clinical comment
		with thiazide-induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk	
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

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

APO-TRIAZIDE 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.

Hydrochlorothiazide

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

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.

10.2. Pharmacodynamics

Hydrochlorothiazide

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.

Triamterene

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 diuresis produced by triamterene alone is limited; it has an additive diuretic effect when used with a thiazide diuretic. Triamterene has no significant pharmacological action other than those on the kidney.

10.3. Pharmacokinetics

Absorption

Hydrochlorothiazide: 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 to 12 hours.

Triamterene: Triamterene is rapidly absorbed from the gastrointestinal tract but to a variable extent (30 to 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 to 4 hours and tapers off 7 to 9 hours after administration.

Distribution

Triamterene: 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.

Elimination

Hydrochlorothiazide: Hydrochlorothiazide is eliminated rapidly by the kidney.

Triamterene: 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.

11. Storage, Stability, and Disposal

Store at room temperature 15°C-30°C.

Keep out of reach and sight of children.

Part 2: Scientific Information

13. Pharmaceutical Information

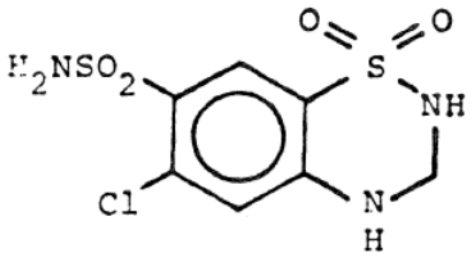
Hydrochlorothiazide

Non-proprietary name of the drug substance: Hydrochlorothiazide

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

Molecular formula and Molecular mass: $C_7H_8ClN_3O_4S_2$ and 297.72 g/mol

Structural formula:



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

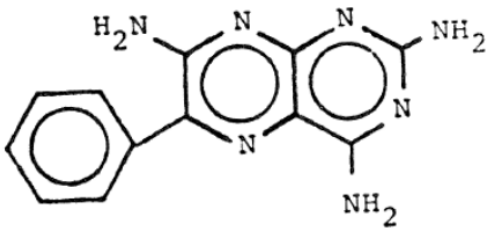
Triamterene

Non-proprietary name of the drug substance: Triamterene

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

Molecular formula and Molecular mass: $C_{12}H_{11}N_7$ and 253.3 g/mol

Structural formula:



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

14. Clinical Trials

14.2. Comparative Bioavailability Studies

A single dose comparative oral bioavailability study of APO-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

	APO-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

	APO-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

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General 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)

Subacute and Chronic Toxicity

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) 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.

Genotoxicity

Hydrochlorothiazide

The mutagenic potential was assessed in a series of *in vitro* and *in vivo* test systems. While some positive results were obtained *in vitro*, all *in vivo* studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential *in vivo*, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

Carcinogenicity

Hydrochlorothiazide

According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the highest dose and adrenal pheocytochroma in one rat study but not in

another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

Reproductive and developmental toxicology

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-TRIAZIDE

triamterene and hydrochlorothiazide tablets

This Patient Medication Information is written for the person who will be taking **APO-TRIAZIDE**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **APO-TRIAZIDE**, talk to a healthcare professional.

Serious warnings and precautions box

APO-TRIAZIDE may cause high levels of potassium in your blood (**hyperkalemia**). You are more likely to develop hyperkalemia if you:

- are 65 years of age or older;
- have diabetes;
- have kidney problems;
- are very ill; or
- are taking other diuretic medicines (used to remove excess salt and water from the body).

While you are taking APO-TRIAZIDE, your healthcare professional may do blood tests to monitor your blood's potassium levels and acidity. They may also check if you have any heart rhythm problems using a test called an electrocardiogram (ECG).

Talk to your healthcare professional **right away** if you have an irregular heartbeat, nausea or vomiting, chest pain, numbness or tingling in the hands, feet or lips, shortness of breath, or weakness or heaviness of the arms or legs.

What APO-TRIAZIDE is used for:

APO-TRIAZIDE is used in adults to:

- treat fluid retention (edema) caused by steroid use, heart, liver or kidney problems, or unknown causes.
- Lower high blood pressure.

How APO-TRIAZIDE works:

APO-TRIAZIDE contains 2 medicinal ingredients, triamterene and hydrochlorothiazide:

- triamterene is a diuretic (also called a "water pill"). It helps the body get rid of excess water and salt by increasing urination, while maintaining normal potassium (an electrolyte) levels in the

blood. This effect also helps to lower blood pressure.
- hydrochlorothiazide is also a diuretic. Similarly, it helps the body get rid of excess water and salt (including potassium). This also helps to lower blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking APO-TRIAZIDE regularly even if you feel fine. Do not stop taking APO-TRIAZIDE without talking to your healthcare professional first.

The ingredients in APO-TRIAZIDE are:

Medicinal ingredients: triamterene and hydrochlorothiazide.

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, and sunset yellow aluminium lake 40 %.

APO-TRIAZIDE comes in the following dosage forms:

Tablets: 50 mg of triamterene / 25 mg of hydrochlorothiazide.

Do not use APO-TRIAZIDE if:

- you are allergic to triamterene, hydrochlorothiazide, or to any of the other ingredients in APO-TRIAZIDE.
- you are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "-MIDE".
- you have difficulty urinating or produce no urine.
- you have severe or worsening kidney or liver problems.
- are breastfeeding or are planning to breast-feed. APO-TRIAZIDE passes into breast milk.
- you have high levels of potassium in your blood (hyperkalemia).
- have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  Because APO-TRIAZIDE contains lactose.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-TRIAZIDE. Talk about any health conditions or problems you may have, including if you:

- are allergic to penicillin, used to treat bacterial infections.
- are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- have diabetes.
- have liver or kidney problems.
- have a history of kidney stones.
- have lupus.
- have high levels of uric acid in the blood or have gout.
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.

- have a history of allergies or bronchial asthma.
- have had or are planning to have a procedure called sympathectomy (cutting or blocking a nerve).
- are pregnant, think you might be pregnant or planning on becoming pregnant.
- have a greater chance of developing skin cancer because you:
    - had skin cancer or have a family history of skin cancer
    - have light-coloured skin
    - sunburn easily
    - take medications to suppress your immune system
- have had breathing or lung problems (including inflammation or fluid in the lungs) in the past following the use of medication containing hydrochlorothiazide. If you experience any severe shortness of breath or difficulty breathing after taking APO-TRIAZIDE, stop the medication and seek medical attention immediately.

Other warnings you should know about:

Eye problems: Hydrochlorothiazide in APO-TRIAZIDE can cause sudden eye disorders:

- **Choroidal effusion:** an abnormal building of liquid in your eye that may result in vision changes.
- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. If left untreated, it may lead to permanent vision loss.

If your vision changes, stop taking APO-TRIAZIDE and seek immediate medical help. These eye disorders are related and can develop within hours to weeks of starting APO-TRIAZIDE.

Risk of skin cancer: APO-TRIAZIDE contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing non-melanoma skin cancer. The risk is higher if you have been taking APO-TRIAZIDE for many years (more than 3) or at a high dose.

While taking APO-TRIAZIDE:
- Make sure to regularly check your skin for any new lesions. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
- Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.
- Talk to your doctor immediately if you get more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) during the treatment.

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

Pregnancy and breast-feeding:
- APO-TRIAZIDE is not recommended during pregnancy as it may harm an unborn child. You and your healthcare professional will decide whether the potential benefits of taking APO-TRIAZIDE outweigh the potential risks to your unborn child. If you discover that you are pregnant during treatment, tell your healthcare professional **right away**.
- APO-TRIAZIDE passes into breast milk. You and your healthcare professional should decide if you

will take APO-TRIAZIDE or breast-feed. **You should not do both.**

Check-ups and testing:

- Your healthcare professional may do tests before, during and after your treatment. These tests may be used to monitor the health of your kidneys and liver, your heart rhythm, the acidity of your blood, the levels of electrolytes in your blood (potassium, chloride, sodium), your blood pressure and the profile of your blood.
- Your healthcare professional may stop your treatment with APO-TRIAZIDE before performing tests to assess the health of your parathyroid glands.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-TRIAZIDE:

- Other medicines used to lower high blood pressure such as guanethidine, methyldopa, ACE inhibitors, ARBs, beta blockers, vasodilators, calcium channel blockers and direct renin inhibitors.
- 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 medication.
- Anticancer medications, such as cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, and sertraline.
- Antidiabetic medications, including insulin and oral medicines.
- Bile acid resins, used to lower cholesterol such as cholestyramine.
- Calcium or vitamin D supplements.
- Corticosteroids, used to treat joint pain and swelling.
- Adrenocorticotropic hormone (ACTH), which may be used to treat diseases such as nephrotic syndrome or collagen diseases and in diagnostic tests.
- Digoxin, a heart medication.
- Medications that slow down or speed up bowel function, such as atropine, metoclopramide, and domperidone.
- Medications used to treat epilepsy, such as carbamazepine and topiramate.
- Gout medications, such as allopurinol and probenecid.
- Lithium, used to treat bipolar disease.
- Non-steroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling such as ibuprofen, naproxen, acetylsalicylic acid and celecoxib.
- Skeletal muscle relaxants, used to relieve muscle spasms-such as tubocurare.
- Potassium supplements, salt substitutes containing potassium or other medicines that may increase serum potassium.

How to take APO-TRIAZIDE:

- APO-TRIAZIDE is not for initial therapy. You must first be stabilized on the individual components of APO-TRIAZIDE (i.e., triamterene and hydrochlorothiazide).
- Take APO-TRIAZIDE exactly as your healthcare professional has told you. Do NOT take more of it

than prescribed.
- It is recommended to take your dose at about the same time every day.
- APO-TRIAZIDE should be taken after a meal.

Usual dose:

- The usual adult dose is 1 tablet twice daily after meals.
- Your healthcare professional may increase or decrease your dose according to your needs.
- Maximum daily dose should not exceed 4 tablets.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-TRIAZIDE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose of your medication, skip your missed dose and take the next dose at your usual scheduled time. Do not double your dose to make up for a missed dose.

Possible side effects from using APO-TRIAZIDE:

These are not all the possible side effects you may have when taking APO-TRIAZIDE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects with APO-TRIAZIDE may include:
- cramping or upset stomach
- muscle spasms
- weakness
- restlessness
- dizziness or feeling like you are spinning (vertigo)
- tingling or "pins and needles" sensations of the skin
- headache
- constipation or diarrhea
- nausea or vomiting
- decreased appetite
- enlargement of the glands in your mouth
- dry mouth
- bleeding under the skin, rash, hives
- yellow hue or tint in your vision
- increased sensitivity to sunlight

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Hypotension (low blood pressure): dizziness, fainting, light-headedness (may occur when you go from lying or sitting to standing up).	√		
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness, generally feeling unwell, muscle spasms, cramping, constipation, fatigue, tingling or numbness.		√	
Non-melanoma skin cancer: lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly.		√	
Uncommon			
Allergic reaction: skin 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.		√	
Hyperglycemia (high blood sugar): frequent urination, thirst, and hunger.	√		
Electrolyte imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat.		√	
Rare			

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Thrombocytopenia (low blood platelets): bruising, bleeding, fatigue and weakness.		√	
Decreased white blood cells: infections, fatigue, fever, aches, pains, and flu-like symptoms.		√	
Very rare			
Acute respiratory distress syndrome (ARDS) (inflammation of lung tissue or excess fluid in the lungs): severe shortness of breath or difficulty breathing, fever, weakness, and confusion.			√
Anemia (decreased number of red blood cells): fatigue, loss of energy, weakness, shortness of breath.		√	
Pancreatitis (inflammation of the pancrease): abdominal pain that lasts and gets worse when you lie down, nausea, vomiting.		√	
Unknown			
Eye disorders: - **Myopia:** sudden near sightedness or blurred vision. - **Glaucoma:** increased pressure in your eyes, eye pain, decrease in vision. **- Choroidal effusion** (buildup of liquid in your eye): blind spots, eye pain, blurred vision.			√
Increased levels of uric acid in the blood: swelling, redness in the joints, sudden and intense attacks of joint pain (gout attack)		√	
Vasculitis (inflammation of the blood vessels): fever, confusion, fatigue, unexplained weight loss, sweats, joint or muscle pain or swelling, numbness, tingling, weakness, a rash of bluish purple spots or blotches.			√
Worsening or activation of lupus: fatigue, fever, joint pain, stiffness and swelling, rash on the face that		√	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
covers the cheeks and the bridge of the nose or rashes elsewhere on the body, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion and memory loss.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature 15°C - 30°C.
- Keep out of reach and sight of children.

If you want more information about APO-TRIAZIDE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products; or by calling 1-800-667-4708.

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