PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMINT-CHLORTHALIDONE

Chlorthalidone Tablets,
Tablets, 12.5 mg, 25 mg, 50 mg, Oral

BP

ATC Code: C03BA04

Diuretic - Antihypertensive

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Date of Initial Authorization:
APR 24, 2025

Submission Control Number: 281585

RECENT MAJOR LABEL CHANGES

None at time of the most recent authorization.

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.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MINT-CHLORTHALIDONE (chlorthalidone tablets) is indicated for:

- Treatment of hypertension. It may be used alone or in association with other antihypertensive agents.

- Adjunctive therapy of edema associated with: renal disease, congestive heart failure of mild to moderate degree (functional class II, III), glomerular filtration rate greater than 30 mL/min; ascites due to cirrhosis of the liver in stable patients; estrogen therapy; corticosteroid therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

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 **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Test**

2 CONTRAINDICATIONS

MINT-CHLORTHALIDONE is contraindicated in:

- Patients with hypersensitivity or suspected hypersensitivity to chlorthalidone and other sulfonamide derivatives or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.**

- Patients with anuria, severe renal failure (creatinine clearance lower than 30 mL/min), severe hepatic failure, refractory hypokalemia or conditions involving enhanced potassium loss, hyponatremia, hypercalcemia, hyperuricemia (history of gout or uric acid calculi), untreated Addison's Disease and concomitant lithium therapy.

- Pregnancy. See **7.1.1 Pregnant Women**.

- Breastfeeding. See **7.1.2 Breastfeeding.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Therapy should be initiated with the lowest possible dose, and be titrated thereafter to gain maximum

therapeutic benefit while keeping side effects to a minimum (e.g., determine the minimum effective maintenance dose for each patient). A single dose daily or every other day given in the morning with food is recommended.

4.2 Recommended Dose and Dosage Adjustment

Hypertension: Usual adult dose is 25 to 50 mg daily. The clinically useful dosage range is 12.5 to 50 mg daily. Doses greater than 50 mg per day increase metabolic complications and are rarely of therapeutic benefit. For a given dose, the full effect is reached after 3 to 4 weeks. For long- term therapy, the lowest possible dosage sufficient to maintain an optimal effect should be employed; this applies particularly to elderly patients.

If the decrease in blood pressure obtained using doses of 25 or 50 mg/day proves inadequate, combined treatment with other antihypertensive drugs (such as beta-blockers) is recommended.

Edema of Specific Origin. See **1 INDICATIONS**: The lowest effective dose is to be identified by titration. Maintenance doses should not exceed 50 mg/day and should be administered over limited periods only. The dosage should be individually adapted to the clinical picture and patient's response.

The therapeutic effect of chlorthalidone occurs even without salt restriction and is well sustained during continued use.

Pediatrics: Health Canada has not authorized an indication for pediatric use.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

Symptoms: Symptoms of chlorthalidone overdosage may include nausea, weakness, dizziness, somnolence, hypovolemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasm.

Treatment: There is no specific antidote. To reduce absorption, induce vomiting or gastric lavage and administer activated charcoal. Intravenous dextrose-saline and potassium chloride may be given, if necessary, with due caution.

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, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 12.5 mg, 25 mg, 50 mg of chlorthalidone	Magnesium Stearate, Microcrystalline Cellulose, Iron oxide yellow, Povidone, Sodium Laurel Sulfate, Sodium Starch Glycolate, Silica colloidal anhydrous.

Tablet: 12.5 mg: Yellow coloured speckled, round, flat face beveled edge (FFBE) tablets debossed with "L" on one side and "1" on other side. Available in Bottles of 100's.

Tablet: 25 mg: Yellow colored, speckled, round, flat face beveled edge (FFBE) tablets debossed with 'L' and '2' on either sides of break line on one side and plain on other side. Available in Bottles of 100's.

Tablet: 50 mg: Yellow colored, speckled, round, flat face beveled edge (FFBE) tablets debossed with 'J' and '5' on either sides of break line on one side and plain on other side. Available in Bottles of 100's.

7 WARNINGS AND PRECAUTIONS

General

The antihypertensive effect of ACE inhibitors is potentiated in the presence of agents that increase plasma renin activity (diuretics). Use of chlorthalidone should be either discontinued or the daily dose reduced when an ACE inhibitor is added to a diuretic agent.

Cardiovascular

A cautious dosage schedule should be adopted in patients with severe coronary arteriosclerosis.

Concomitant administration of chlorthalidone and digitalis requires caution. Electrolytes and digitalis levels should be monitored closely. Adjustment of digitalis/chlorthalidone dosing or provision of supplemental potassium may be required. Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digitalis toxicity, which may lead to fatal arrhythmic events.

Driving and Operating Machinery

Occupational hazards: Because dizziness and impaired patient reaction time are possible side effects of chlorthalidone, especially at the start of therapy, patients should be warned about the possible hazards of operating machines or driving motor vehicles.

Endocrine and Metabolism

Metabolic Effects: Chlorthalidone may raise the serum uric acid level, but attacks of gout (in predisposed patients) are rarely observed during chronic treatment. In cases where prolonged and significant elevation of blood uric acid concentrations is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Small and partially reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is equivocal. Chlorthalidone should not be used as a first-line drug for long-term treatment in patients with hypercholesterolemia. If chlorthalidone must be used, serum lipids should be regularly monitored. If there is a rise in lipid levels, withdrawal of chlorthalidone should be considered.

Chlorthalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus, chlorthalidone may impair glucose tolerance. Increases in serum glucose may occur. Close monitoring of glycaemia is recommended in the initial phase of therapy and in prolonged therapy, tests for glucosuria should be carried out at regular intervals.

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. Discontinue thiazides and their analogues before carrying out tests for parathyroid function.

Hepatic/Biliary/Pancreatic

In patients with impaired hepatic function or progressive liver disease, caution should be exercised since even minor alterations in fluid and electrolyte balance or of serum ammonia may precipitate hepatic coma.

Should be used with caution in patients with impaired hepatic function. See **2 CONTRAINDICATIONS**.

Immune

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics, which are structurally related to chlorthalidone. However, systemic lupus erythematosus has not been reported following chlorthalidone administration.

Monitoring and Laboratory Tests

Fluid status and Serum Electrolytes

Patients receiving thiazides and their analogues should be carefully observed for clinical signs of fluid and electrolyte imbalance. As chlorthalidone is a diuretic, an inappropriately high dose can cause severe volume depletion. Serum sodium, potassium, chloride, and calcium levels should be checked periodically to detect possible electrolyte disturbances. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, cardiac arrhythmias or corresponding

ECG changes and gastrointestinal disturbances such as nausea and vomiting.

Close monitoring of fluid status and serum electrolytes is indicated particularly in older patients, in patients receiving digitalis preparations for cardiac failure, those taking an abnormal (low in potassium) diet in patients suffering from gastrointestinal complaints, vomiting excessively or receiving parenteral fluids, patients with ascites due to liver cirrhosis, and in patients with edema due to nephrotic syndrome. For the latter condition, chlorthalidone should be used only under close control in normokalemic patients with no signs of volume depletion or severe hypoalbuminemia.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. In all combination treatment regimens, maintenance or normalization of the potassium balance should be closely checked. If hypokalemia is accompanied by clinical signs (e.g., muscular weakness, paresis and ECG alteration), chlorthalidone should be discontinued.

As with thiazide diuretics, kaluresis induced by chlorthalidone is dose dependent, and there is inter-individual variability in magnitude. With chlorthalidone dosing at 25 mg/day, serum potassium concentration decreases an average of 0.5 mmol/L. If chronic treatment with chlorthalidone is contemplated, serum potassium concentrations should be determined initially, and then 3 to 4 weeks later. If, thereafter, potassium balance is not disturbed further, concentrations should be assessed every 4 to 6 months. Conditions that may alter potassium balance (especially in the presence of brisk diuresis) include: vomiting, diarrhea, malnutrition, change in renal function (e.g., nephrosis), liver cirrhosis, hyperaldosteronism, or concomitant use of corticosteroids or ACTH.

Titrated co-administration of an oral potassium salt (e.g., KCl) may be considered in patients: receiving digitalis; exhibiting signs of coronary heart disease (unless they are also receiving an ACE inhibitor); on high doses of a beta-adrenergic agonist; whose plasma potassium concentrations are less than 3.0 mmol/L. Combined treatment consisting of chlorthalidone and a potassium salt or a potassium-sparing diuretic must be avoided in patients also receiving ACE inhibitors. See **9.4 Drug-Drug Interactions, ACE Inhibitors.**

If oral potassium preparations are not tolerated, chlorthalidone may be combined with a potassium-sparing diuretic (e.g., triamterene).

Excessively strict low-salt diets should be avoided. Hyponatremia, accompanied by neurological symptoms (nausea, debility, progressive disorientation, apathy), has been observed in isolated cases.

Should hypochloremic alkalosis or hyponatremia occur, consider appropriate therapy. Water restriction rather than actual salt replacement may be considered appropriate treatment of any chloride deficit except in rare instances when hyponatremia is life threatening, then appropriate salt replacement is the therapy of choice.

Magnesium levels:

Patients receiving relatively high doses of thiazides or their analogues may develop hypomagnesemia accompanied by such signs and symptoms as nervousness, muscle spasm, and cardiac arrhythmias.

Uric Acid Levels:

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

Serum glucose levels:

Serum glucose levels may increase with chronic use.

Thiazides may decrease protein bound iodine levels without signs of thyroid disturbance.

Neurologic

A cautious dosage schedule should be adopted in patients with severe cerebral arteriosclerosis.

Ophthalmologic

Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma

Chlorthalidone is a thiazide-like diuretic. Thiazide diuretics, which are sulfonamides, can cause an idiosyncratic reaction resulting in choroidal effusion associated with acute transient myopia and/or acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to a week of a drug initiation. Untreated acute- angle glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the chlorthalidone as rapidly as possible. Prompt medical or surgical treatment 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.

Peri-Operative Considerations

Treatment with thiazide diuretics should be initiated cautiously in postsympathectomy patients since the antihypertensive effects may be enhanced.

Renal

Chlorthalidone should be used with caution in patients with renal disease, as its use may precipitate azotemia. See **2 CONTRAINDICATIONS**. Because of the possibility of progression of renal damage, periodic determination of the BUN and serum creatinine are indicated. Should there be an elevation of either parameter, treatment should be discontinued. Like thiazides, chlorthalidone may lose its diuretic efficacy when glomerular filtration rate drops below 30 mL/min, a point at which treatment with loop diuretics may be more appropriate.

Sensitivity/Resistance

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

Skin

Photosensitivity

During treatment with chlorthalidone, long-term sun exposure is not recommended, as there is a risk of

occurrence of photosensitivity symptoms.

7.1 Special Populations

7.1.1 Pregnant Women

Chlorthalidone, like other diuretics, can cause placental hypoperfusion. Since they do not prevent or alter the course of EPH (edema, proteinuria, hypertension)-gestosis (pre-eclampsia), these drugs must not be used to treat hypertension in pregnant women. The use of chlorthalidone for other indications (e.g., Adjunctive therapy of edema associated with congestive heart failure of mild to moderate degree (functional class II, III)) is also contraindicated. See **2 CONTRAINDICATIONS**.

Chlorthalidone crosses the placental barrier. Levels in fetal whole blood were about 15% of those found in the maternal blood of mothers receiving 50 mg chlorthalidone daily pre- and postpartum. Concentration in amniotic fluid is approximately 4% of maternal blood levels.

7.1.2 Breast-feeding

Thiazide-like diuretics, like chlorthalidone, are excreted in human milk. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, use in lactating mothers is contraindicated. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. See **2 CONTRAINDICATIONS**.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.**

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Serious adverse reactions:
Serious adverse reactions include cardiac arrhythmia, dyspnea, aplastic anemia and agranulocytosis.

Most frequent adverse reactions (≥10%):
The most frequent adverse reactions include hypokalemia, hyperuricemia, and hyperlipidemia.

Other adverse reactions are listed below by system organ class and frequency. Frequency estimates are as follows: very common: ≥10%, common: ≤1 to <10%, uncommon: ≤0.1% to <1%, rare: ≤0.01 to≤0.1% and very rare: <0.01%.

Blood and lymphatic system disorders:

Rare: thrombocytopenia, leukopenia and eosinophilia.

Eye disorders:

Rare: disturbances of vision.

Not known: Choroidal effusion, acute myopia and acute angle-closure glaucoma (Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics).

Gastrointestinal disorders:

Common: minor gastrointestinal distress.

Rare: mild nausea and vomiting, gastric pain, constipation, and diarrhea.

Very rare: pancreatitis.

Hepatobiliary disorders:

Rare: intrahepatic cholestasis or jaundice.

Investigations:

Common: decreased reaction time.

Metabolism and nutrition disorders:

Common: hyponatremia, hypomagnesemia, hyperglycemia and loss of appetite.

Uncommon: gout.

Rare: hypercalcemia, worsening of diabetic metabolic state.

Very rare: hypochloremic alkalosis.

Nervous system disorders:

Common: dizziness, slow mentation.

Rare: paresthesia, headache.

Renal and urinary disorders:

Rare: glycosuria, allergic interstitial nephritis.

Reproductive system and breast disorders

Common: impotence.

Respiratory, thoracic and mediastinal disorders:

Rare: idiosyncratic pulmonary edema (respiratory disorders).

Skin and subcutaneous tissue disorders:

Common: urticaria and other forms of skin rash.

Rare: photosensitivity.

Vascular disorders:

Common: postural hypotension, which may be aggravated by alcohol, anesthetics or sedatives.

Very rare: vasculitis.

8.5 Post-Market Adverse Reactions

Information is not available.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Consuming alcohol may modify the effect of this product. Limit alcohol consumption during treatment.

Patients should also be cautioned that taking alcohol can increase the chance of dizziness and cause the blood pressure to fall even more.

Orthostatic hypotension may occur when taking MINT-CHLORTHALIDONE and may be aggravated by alcohol, anesthetics or sedatives.

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

Common name	Source of Evidence	Effect	Clinical comment
ACE inhibitors	T	The antihypertensive effect of ACE inhibitors is potentiated in the presence of agents that increase plasma renin activity (diuretics).	A cautious dosage schedule should therefore be adopted when an ACE inhibitor is added to a diuretic agent.
Alcohol, barbiturates and narcotics	C	Potentiation of orthostatic hypotension may occur	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Allopurinol	T	Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of allopurinol may be required.
Amantadine	T	Co-administration of thiazide diuretics may increase the risk of adverse effects from amantadine.	
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Anticholinergics (e.g., atropine, biperiden)	T	The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and rate of gastric emptying.	Dose adjustment of thiazide may be required.
Antihypertensive Agents	T	Diuretics potentiate the action of antihypertensive agents (e.g., methyldopa, beta-blockers, vasodilators, calcium antagonists, ACE inhibitors).	Careful monitoring of the doses is required until the patient is stabilized.
Antineoplastic Agents (e.g., cyclophosphamide, methotrexate)	T, C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance the myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.

Common name	Source of Evidence	Effect	Clinical comment
Bile acid sequestrants, e.g. Cholestyramine and colestipol resins	T	Absorption of thiazide diuretics is decreased by cholestyramine because Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43- 85%., A decrease in pharmacological effect may be expected.	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 or Vitamin D supplements	T C	Concomitant use of thiazide diuretics may decrease urinary excretion of calcium, and co-administration of Vitamin D may potentiate the increase in serum calcium. Concomitant use of thiazide-type diuretics may cause hypercalcemia by increasing tubular calcium reabsorption.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements, and signs of hypercalcemia. Dose reduction and/or withdrawal of calcium and/or Vitamin D supplements may be necessary.
Corticosteroids and Adrenocorticotropic hormone (ACTH)	T	The hypokalemic effects of diuretics may be increased by corticosteroids, ACTH and amphotericin.	Monitor serum potassium, and adjust medications, as required.
Curare Derivatives and Ganglionic Blocking Agents	T	Thiazides may increase responsiveness to curare derivatives and ganglionic blocking agents.	
Cyclosporin	T	Concomitant treatment with diuretics may increase the risk of hyperuricemia and gout-type complications.	
Diazoxide	T	Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.	
Digitalis	CT, T	Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digitalis-induced toxicity, which may lead to fatal arrhythmic events. See **7 WARNINGS AND PRECAUTIONS**.	Concomitant administration of chlorthalidone and digitalis requires caution. Monitor electrolytes and digitalis levels closely. Supplement potassium or adjust doses of digitalis or chlorthalidone, as required.

Common name	Source of Evidence	Effect	Clinical comment
Insulin and Oral Antidiabetic Agents	CT T	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. It may be necessary to adjust the dosage of insulin or oral antidiabetic agents in response to changes in glucose tolerance that chlorthalidone may produce. See **7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism.**
Lithium	T	Diuretics enhance the cardiotoxic (manifested in ECG changes) and neurotoxic (manifested by ataxia, confusion, and mental disorientation) effects of lithium and these drugs should not be administered concurrently.	In those rare instances when these drugs must be given together, patients should be observed closely for signs and symptoms of lithium toxicity. Close monitoring of serum electrolytes and lithium concentrations and maintenance of adequate fluid, potassium and sodium intake are also necessary.
NSAIDs	CT	Concomitant administration of certain NSAIDs (e.g., indomethacin) may weaken the diuretic and antihypertensive activity of thiazides, and there have been isolated reports of a deterioration of renal function in predisposed patients.	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required.

Legend: C = Case 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

Chlorthalidone inhibits reabsorption of sodium and chloride in the distal renal tubule thus promoting water loss. The higher urine volume increases potassium loss. Little information is available on the absorption of the drug. Its long elimination half-life and clinical experience place it as a long-acting thiazide derivative. This may not be important clinically because the biological effects of thiazides particularly as antihypertensives may be prolonged compared to their elimination rate. The longer acting agents appear to cause increased potassium loss. Although a mild diuretic, its combination with loop diuretics is particularly potent because the latter presents much more sodium chloride to the distal tubule.

The blood pressure lowering effects are initially due to volume reduction but the persisting effect includes other undetermined mechanisms that reduce peripheral resistance. A high salt intake reverses its antihypertensive effect.

10.2 Pharmacodynamics

Chlorthalidone is a benzothiadiazine (thiazide)-related diuretic with a long duration of action.

Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting $NaCl^-$ reabsorption (by antagonising the $Na+Cl^-$ cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collection tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

In persons with normal renal function, diuresis is induced after the administration of 12.5mg chlorthalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in oedematous patients. The diuretic effect sets in after 2 to 3 hours, reaches its maximum after 4 to 24 hours and may persist for 2 to 3 days.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.

In hypertensive individuals, chlorthalidone gently reduces blood pressure. On continued administration the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of chlorthalidone is dose dependent between 12.5 and 50mg/day. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when chlorthalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including chlorthalidone, reduces cerebrovascular (stroke) coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other antihypertensives potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

In renal diabetes insipidus, chlorthalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

10.3 Pharmacokinetics

Absorption

The bioavailability of an oral dose of 50 mg chlorthalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50 mg, C_{max} values average 1.5mcg/mL (4.4 microcmol/L) and 3.2 mcg/mL (9.4 micromol/L) respectively. For doses up to 100 mg there is a proportional increase in AUC. On repeated daily doses of 50 mg, mean steady-state blood concentrations of 7.2 mcg/mL (21.2 micromol/L), measured at the end of the 24 to hour dosage interval, are reached after 1 to 2 weeks.

Distribution:

In blood, only a small fraction of chlorthalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlorthalidone in whole blood was found in plasma at steady state during treatment with 50 mg doses. In vitro, plasma protein binding of chlorthalidone is about 76% and the major binding protein is albumin.

Chlorthalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50 mg chlorthalidone daily before and after delivery, chlorthalidone levels in foetal whole blood are about 15% of those found in maternal blood. Chlorthalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Metabolism:

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and in the faeces, mainly in unchanged form.

Elimination

The major portion of an absorbed dose of chlorthalidone from whole blood and plasma is excreted by the kidneys with an elimination half-life averaging 50 hours. The elimination half- life is unaltered after chronic administration. The major part of an absorbed dose of chlorthalidone is excreted by the kidneys, with a mean renal clearance of 60 ml/min.
Metabolism and hepatic excretion into the bile constitute a minor way of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and in the feces, mainly in an unchanged form.

Special Populations and Conditions

- Geriatrics In elderly patients, the elimination of chlorthalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlorthalidone.

- Renal Insufficiency Renal dysfunction does not alter the pharmacokinetics of chlorthalidone, the rate limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes. No dosage adjustment is needed in patients with impaired renal function.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C).

MINT-CHLORTHALIDONE should never be disposed of in household trash. Disposal via a pharmacy Take-back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

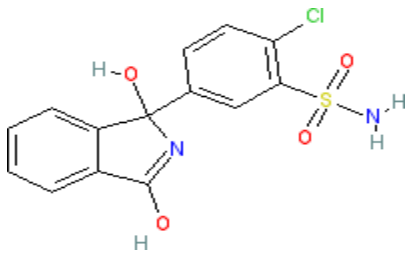
Drug Substance

Proper name: Chlorthalidone

Chemical name: 2-chloro-5-(1,3-dihydroxy-1H-isoindol-1-yl)benzene-1-sulfonamide

Molecular formula and molecular mass: $C_{14}H_{11}ClN_2O_4S$ and 338.8

Structural formula:



Physicochemical properties:

Physical Form**:** White or yellowish-white powder, practically insoluble in water and methylene chloride, but soluble in acetone and in methanol.

Partition Coefficient: 1.3

Ionisation constant(pKa): 9.4

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorised is not available.

14.2 Comparative Bioavailability Studies

A single-dose, randomized, two-way crossover bioavailability study of Chlorthalidone 50 mg Tablets (Mint Pharmaceuticals Inc.) and [Pr]Chlorthalidone Tablets BP 50 mg (AA Pharma Inc.) was performed in healthy male subjects under fasting conditions. Comparative bioavailability data from 34 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOEQUIVALENCE DATA

Chlorthalidone (1 x 50 mg Tablet) Geometric Mean Arithmetic Mean (%CV)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{72} (ng·h/mL)	5671.65 5910.39 (28.2%)	5309.22 5449.4 (23.4%)	106.8	100.3% - 113.8%
C_{max} (ng/ml)	261.48 272.80 (27.5%)	244.65 249.378 (20.3%)	106.9	98.5% - 116.0%
T_{max}[3] (h)	2.875 (1.00 - 5.00)	2.900 (1.00 - 5.00)		
$T_{1/2}$[4]	-	-		

[1]Chlorthalidone 50 mg Tablets, Mint Pharmaceuticals Inc., Canada
[2Pr]Chlorthalidone Tablets BP 50 mg, AA Pharma INC., Toronto, Canada
[3]Expressed as the median (range) only
[4]Since the AUC_{72} parameter was applied, a meaningful characterization of the terminal elimination phase of chlorthalidone was not possible. On this basis, the $T_{1/2}$ parameter was not reported.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Information is not available.

Carcinogenicity: Information is not available.

Genotoxicity: Information is not available.

Reproductive and Developmental Toxicology:

Chlorthalidone had no effect on fertility in rats. Reproduction studies have been performed in the rat and the rabbit at doses up to 420 times the human dose and have revealed no evidence of harm to the fetus due to chlorthalidone.

Special Toxicology: Information is not available.

Juvenile Toxicity: Information is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1 EDARBYCLOR® Tablets; azilsartan medoxomil potassium and chlorthalidone 40 mg/12.5 mg, 80 mg/12.5 mg and 40 mg/25 mg; Submission Control 246568 Product Monograph Bausch Health, Canada Inc. July 12, 2021

2 TENORETIC® Tablets; atenolol and chlorthalidone tablets 50/25 mg and 100/25 mg Submission Control 190685 Product Monograph AstraZeneca Canada, Inc. July 12, 2016

3 PRAPO -CHLORTHALIDONE Tablets 50 mg, Submission Control 272147, Product Monograph, Apotex Inc. March 14, 2023

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]MINT-CHLORTHALIDONE

Chlorthalidone tablets BP

Read this carefully before you start taking **MINT-CHLORTHALIDONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MINT-CHLORTHALIDONE**.

What is MINT-CHLORTHALIDONE used for?

MINT-CHLORTHALIDONE is used in adults to:

- lower high blood pressure. It can be used alone or with other blood pressure lowering medicines.
- help reduce swelling (fluid retention) caused by kidney, liver and heart problems, and also due to treatment with some medicines including estrogen and corticosteroids.

How does MINT-CHLORTHALIDONE work?

MINT-CHLORTHALIDONE contains the medicinal ingredient chlorthalidone which belongs to a group of medicines called thiazide diuretics. Thiazide diuretics help to reduce the amount of water in your body. They do this by increasing the amount of water that you pass as urine. They are sometimes called 'water pill'.

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

What are the ingredients in MINT-CHLORTHALIDONE?

Medicinal ingredients: chlorthalidone

Non-medicinal ingredients: colloidal silicon dioxide, D&C yellow #10, FD&C yellow #6, magnesium stearate and microcrystalline cellulose

MINT-CHLORTHALIDONE comes in the following dosage forms:

Tablet: 12.5 mg, 25 mg and 50 mg

Do not use MINT-CHLORTHALIDONE if:

- you are allergic to chlorthalidone or sulphonamide derivatives such as sulfamethoxazole or any other ingredients in MINT-CHLORTHALIDONE (see **What are the ingredients in MINT-CHLORTHALIDONE.**).

- you have severe kidney or liver problems.
- you are unable to pass urine.
- you have any conditions that cause increased potassium loss.
- you have low blood levels of sodium.
- you have high blood levels of calcium.
- you have high blood levels of uric acid.
- you have ever had gout or kidney stones.
- you have Addison's Disease, a condition involving your adrenal glands, the glands located above your kidneys, and are not being treated for it.
- you are taking lithium, used to treat bipolar disorder.
- you are pregnant or planning to become pregnant.
- you are breastfeeding. MINT-CHLORTHALIDONE passes into breastmilk.

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

- have any other liver or kidney problems.
- have heart problems.
- are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
- are on a low-salt diet.
- are allergic to penicillin.
- have asthma or allergies.
- have low blood levels of potassium, sodium, chloride, magnesium or phosphate.
- have problems with your thyroid and parathyroid glands.
- have ever had gout attacks.
- have high cholesterol levels.
- have diabetes (increased levels of sugar in the blood).
- have changes in your blood ammonia levels.
- have lupus, an auto-immune disease.
- have recently had a sympathectomy, a procedure to treat severe excess sweating (hyperhidrosis).
- have thickening and hardening of the walls of the arteries in the heart or brain.
- are also taking an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in "PRIL". It lowers blood pressure.
- are taking digitalis, a medicine used to treat heart problems.
- are elderly.

Other warnings you should know about:

Sudden eye problems: MINT-CHLORTHALIDONE can cause serious eye problems. These eye problems are related and can happen within hours to weeks of starting MINT-CHLORTHALIDONE. These eye problems include:

- **Choroidal effusion**: An abnormal buildup 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. Untreated, it may lead to permanent vision loss.

If your vision changes, stop taking MINT-CHLORTHALIDONE and get immediate medical help.

Driving and using machines: MINT-CHLORTHALIDONE can cause dizziness and can affect your reaction time, especially when you first start taking it. Give yourself time after taking MINT-CHLORTHALIDONE to see how you feel before driving a vehicle or using machinery.

Blood tests and monitoring: MINT-CHLORTHALIDONE can cause abnormal blood and urine test results, including changes to your electrolyte and cholesterol levels and increased amounts of sugar in your urine. Your healthcare professional will decide when to perform blood and urine tests and will interpret the results.

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 MINT-CHLORTHALIDONE:

- other medicines used to lower high blood pressure or treat heart problems such as:
  - ACE inhibitors (for example, lisinopril),
  - beta blockers (for example propranolol hydrochloride),
  - guanethidine, methyldopa,
  - vasodilators (for example bosentan),
  - calcium channel blockers (for example amlodipine).
- alcohol, barbiturates (sleeping pills) and narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- allopurinol - used to treat gout.
- amantadine - used to treat Parkinson's disease or viral infections.
- amphotericin B - used to treat fungal infections.
- anticholinergics such as atropine or biperiden - for abdominal or stomach spasms or cramps.
- medicines used to treat cancer, such as cyclophosphamide or methotrexate.
- bile acid resins such as cholestyramine - used to lower cholesterol.
- vitamin D or calcium supplements.
- corticosteroids such as prednisolone or betamethasone - used to treat joint pain and swelling.
- adrenocorticotropic hormone (ACTH) - used to treat West Syndrome.
- skeletal muscle relaxants used to relieve muscle spasms, including tubocuranine.
- ganglionic blocking agents – used for high blood pressure.
- cyclosporin - used to supress the immune system after a transplant or in other conditions with inflammation.
- diazoxide - used to treat low blood sugar.
- digitalis – used for an irregular heartbeat.
- insulin and oral medicines for diabetes such as chlorpropamide or glibenclamide.
- lithium - used to treat bipolar disease.
- non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or indomethacin - used to reduce pain and swelling.

How to take MINT-CHLORTHALIDONE:

- Follow the directions given to you by your healthcare professional.
- Your healthcare professional will decide on the dose that is right for you based on your particular

condition and will monitor your progress. If necessary, this dose can be changed.
- Take MINT-CHLORTHALIDONE tablets in the morning with food. Swallow your tablets whole with a drink of water.

Usual dose:

High blood pressure:

The usual adult dose is 25 mg (half a tablet) to 50 mg (one tablet) a day. The maximum daily dose is 50 mg a day.

Swelling (fluid retention):

Your healthcare professional will start with lowest possible dose. Your dose should not exceed 50 mg (one tablet) per day.

Elderly patients:

Your healthcare professional will give you the lowest possible dose to avoid side effects.

Overdose:

Symptoms of MINT-CHLORTHALIDONE overdose may include nausea, weakness, dizziness, sleepiness, decrease in the volume of blood or fluids in the body, low blood pressure and electrolyte disturbances causing irregular heartbeat and muscle spasms.

If you think you, or a person you are caring for, have taken too much MINT-CHLORTHALIDONE, 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, take it as soon as you remember. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do NOT take a double dose to make up for a missed dose.

What are possible side effects from using MINT-CHLORTHALIDONE?

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

Side effects may include:

- loss of appetite
- nausea, vomiting
- diarrhea
- stomach pain
- constipation
- dizziness
- headache
- pins and needles sensation
- rash
- hives

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hypokalemia (low blood levels of potassium): muscle weakness, muscle twitching, fast or irregular heartbeat		✓	
Hyperuricemia (high blood levels of uric acid, gout): severe joint pain, stiffness, redness and swelling		✓	
COMMON			
Hyponatremia (low blood levels of sodium): tiredness, confusion, muscle twitching, fits, coma		✓	
Hypomagnesemia (low blood levels of magnesium): nervousness, muscle spasm, irregular heartbeat		✓	
Hyperglycemia (high blood sugar levels): tiredness, weakness, feeling thirsty		✓	
Low blood pressure: dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up.		✓	
Impotence: inability to have or maintain an erection	✓		
RARE			
Hypercalcemia (high blood levels of calcium): agitation, sore eyes, abdominal pain, nausea, vomiting, constipation		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Photosensitivity: increased sensitivity of your skin to sunlight	✓		
Liver problems: yellowing of the skin or eyes, dark urine, pale stool, abdominal pain, nausea, vomiting, loss of appetite		✓	
Heart rhythm problems: irregular heartbeat, palpitations, fainting			✓
Thrombocytopenia (low blood levels of platelets): increased bruising or bleeding, fatigue, weakness		✓	
Leukopenia and Agranulocytosis (**low levels of white blood cells):** fever, chills, sore throat, faster heartbeat and breathing, other signs of infection			✓
Eosinophilia (high blood levels of eosinophils): rash, Itching		✓	
Aplastic anemia (low levels of all blood cells): fatigue, shortness of breath, frequent infections, rapid heartbeat, pale skin, bleeding			✓
Eye problems: **- Choroidal effusion**: blind spots, eye pain, blurred vision **- Myopia:** sudden near sightedness or blurred vision **Glaucoma:** increased pressure in your eye, eye pain			✓
VERY RARE			
Hypochloremic alkalosis (low levels of chloride in the blood): dry mouth, thirst, nausea, vomiting, weakness, drowsiness, restlessness, seizures or fits, confusion, headache, muscle pains or cramps, dizziness, lightheadedness or fainting		✓	
Pancreatitis (inflammation of the pancreas): severe stomach pain that lasts and gets worse when you lie down, nausea, vomiting		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Breathing problems: trouble breathing, shortness of breath			✓
Kidney problems: decreased urination, nausea, vomiting, swelling of the extremities, fatigue		✓	
Inflammation of the blood vessels: pain, swelling, redness and inflammation of a vein in the arm or leg		✓	

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 health 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 to 30°C).

Keep out of reach and sight of children.

If you want more information about MINT-CHLORTHALIDONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.mintpharma.com), or by calling 1-877-398-9696

This leaflet was prepared by Mint Pharmaceutical Inc.

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