AUSTRALIAN PRODUCT INFORMATION

Hygroton® 25
Chlortalidone
Tablet

1 NAME OF THE MEDICINE

Chlortalidone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hygroton tablet contains 25 mg of chlortalidone as the active ingredient.

Excipients with known effect: lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Hygroton tablets are pale orange, speckled, round flat tablets with bevelled edges. One side bears the imprint "CW" and a score line, nothing on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Essential arterial hypertension, as long as creatinine clearance is > 30 mL/min; as primary therapy or in combination with other antihypertensive agents.
- Stable, chronic heart failure of mild to moderate degree (functional class II, III), as long as creatinine clearance is > 30 mL/min.
- Ascites due to cirrhosis of the liver in stable patients under close control.

4.2 DOSE AND METHOD OF ADMINISTRATION

As with all diuretics, therapy should be initiated with the lowest possible dose. This dose should be titrated according to the individual patient's response to gain maximum therapeutic benefit while keeping side effects to a minimum.
A single dose daily or every other day given in the morning with food is recommended.

Hypertension

Adults

The range of clinically useful doses is 12.5 to 50 mg/day. Recommended starting doses are either 12.5 or 25 mg/day, the latter being sufficient to produce the maximum hypotensive effect in most patients. For a given dose, the full effect is reached after 3 to 4 weeks. If the decrease in blood pressure proves inadequate with 25 or 50 mg/day, combined treatment with other antihypertensive medicines (such as beta-blockers, ACE inhibitors or angiotensin II inhibitors) is recommended. When adding an ACE inhibitor or angiotensin II inhibitors, Hygroton 25 should be reduced or discontinued (see Section 4.4 Special warnings and precautions for use).

Stable, chronic heart failure (functional class II/III)

Adults

The recommended starting doses are 25 to 50 mg/day. In patients with severe chronic heart failure (grade IV) not tolerating loop diuretics, initial doses of two 50 mg tablets of Hygroton 25 may be given every other day. For maintenance, use the lowest effective dose: 12.5 to 50 mg/day or 25 to 50 mg every other day. If the response proves inadequate, a positive inotropic medicine (e.g. digitalis), possibly combined with an ACE inhibitor, may be added. In the latter case, Hygroton 25 is to be reduced or discontinued (see Section 4.4 Special warnings and precautions for use).

Oedema of specific origin (see Section 4.1 Therapeutic indications)

Adults

The lowest effective dose is to be identified by titration and administered over limited periods only. Doses should not exceed 50 mg/day.

Children

The lowest effective dose should also be used in children. For example, an initial dose of 0.5 to 1 mg/kg/48 hours and a maximum dose of 1.7 mg/kg/48 hours have been used.

4.3 CONTRAINDICATIONS

- Anuria, severe renal failure (creatinine clearance lower than 30 mL/min) and hepatic failure.
- Hypersensitivity to chlortalidone and other sulfonamide derivatives or to any of the excipients in Hygroton 25.
- Refractory hypokalaemia, hyponatraemia and hypercalcaemia.
- Symptomatic hyperuricaemia (history of gout or uric acid calculi).
- Hypertension during pregnancy.
- Conditions involving enhanced potassium loss, e.g., salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function.
- Untreated Addison's disease.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Renal and hepatic impairment

Hygroton 25 should be used with caution in patients with renal disease or with impaired hepatic function (see Section 4.3 Contraindications).

Thiazides may precipitate azotaemia in patients with severe renal disease, and the effects of repeated administration may be cumulative.

Hygroton 25 and other thiazide diuretics lose their diuretic effect when the creatinine clearance is < 30 mL/min. In these cases loop diuretics are indicated.

In patients with impaired hepatic function or progressive liver disease, especially in patients with liver cirrhosis, minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulphonamide, or sulphonamide derivatives such as chortalidone can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue chlortalidone 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.

Electrolytes
Treatment with thiazide diuretics has been associated with electrolyte disturbance such as hypokalaemia, hypomagnesaemia, hypercalcaemia and hyponatraemia. Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

As with all thiazide diuretics, kaluresis induced by Hygroton 25 is dose-dependent and varies in extent from one subject to another. With 25 mg/day, the decrease in serum potassium concentrations averages 0.7 mmol/L. For chronic treatment, serum potassium concentrations should be checked initially and then after 3 to 4 weeks. Thereafter, if the potassium balance is not disturbed by additional factors (e.g. vomiting, diarrhoea, change in renal function, etc.), checks should be carried out every 4 to 6 months.

Titrated co-administration of an oral potassium salt (e.g. KCl) may be considered in patients receiving digitalis; in patients exhibiting signs of coronary heart disease, unless they are also receiving an Angiotensin Converting Enzyme (ACE) inhibitor; in patients on high doses of a beta-adrenergic agonist; and in all cases where plasma potassium concentrations are < 3.0 mmol/L. If oral potassium preparations are not tolerated, Hygroton 25 may be combined with a potassium-sparing diuretic (e.g. triamterene).

In all cases of combined treatment, maintenance or normalisation of the potassium balance should be checked closely. If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis and ECG alteration), Hygroton 25 should be discontinued.
Combined treatment consisting of Hygroton 25 and a potassium salt or a potassium-sparing diuretic must be avoided in patients also receiving ACE inhibitors or angiotensin II inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions**)**.

Hyponatraemia, accompanied by neurological symptoms (nausea, debility, progressive disorientation, apathy), has been observed in isolated cases.

Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with oedema due to nephrotic syndrome. For the latter condition, Hygroton 25 should be used only under close control in normokalaemic patients with no signs of volume depletion or severe hypoalbuminaemia.

Metabolic effects
Chlortalidone may raise the serum uric acid level, but attacks of gout are rarely observed during chronic treatment.

Although glucose tolerance may be adversely affected, diabetes mellitus very seldom occurs under treatment.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatments with thiazides and thiazide-like diuretics. The clinical relevance of these findings is not clear.

Hygroton 25 should not be used as a first-line medicine for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).

Combination with an ACE inhibitor or angiotensin II inhibitor
The antihypertensive effect of ACE inhibitors or angiotensin II inhibitors is potentiated by agents that increase plasma renin activity (diuretics). A cautious dosage schedule should therefore be adopted when an ACE inhibitor or angiotensin II inhibitor is added to a diuretic agent. It is recommended that the diuretic be reduced in dosage or withdrawn for 2-3 days and that a low initial dose of the ACE inhibitor or angiotensin II inhibitor be used.

Use in the elderly
Elimination is slower in elderly patients than in young, healthy adults, although absorption is the same. Consequently, close medical observation including monitoring of serum electrolytes is essential when treating elderly patients with Hygroton 25 (see Section 5.2 Pharmacokinetics and Section 4.4 Special warnings and precautions for use - Electrolyes).

Paediatric use
No data available.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Lithium: Since diuretics raise blood lithium levels, the latter must be monitored in patients under lithium therapy who are taking Hygroton 25 at the same time. Where lithium has induced polyuria, diuretics may exert a paradoxical antidiuretic effect.

Non-depolarising relaxants, curare derivatives and antihypertensive medicines: Diuretics potentiate the action of non-depolarising relaxants, curare derivatives and

antihypertensive medicines (e.g. guanethidine, methyldopa sesquihydrate, beta-blockers, vasodilators, calcium antagonists, ACE inhibitors or angiotensin II inhibitors).

Corticosteroids, ACTH, beta-2 agonists, amphotericin B (amphotericin), and carbenoxolone: The hypokalaemic effect of diuretics, with risk of heart and/or muscle disorders may be increased by corticosteroids, ACTH, beta-2 agonists, amphotericin B (amphotericin), and carbenoxolone.

Insulin and oral antidiabetic agents: It may prove necessary to adjust the dosage of insulin and of oral antidiabetic agents (see Section 4.4 Special warnings and precautions for use – Metabolic effects).

Digitalis: Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis-induced cardiac arrhythmias (see Section 4.4 Special warnings and precautions for use).

Non-steroidal anti-inflammatory drugs: Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indometacin) may weaken the diuretic and antihypertensive activity of diuretics, and there have been isolated reports of a deterioration in renal function in predisposed patients.

Allopurinol: Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Co-administration of thiazide diuretics may increase the risk of adverse effects from amantadine.

Antineoplastic agents (e.g. cyclophosphamide monohydrate, methotrexate): Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance the myelosuppressive effects.

Anticholinergics (e.g. atropine, biperiden): The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and stomach emptying rate.

Anion exchange resins (e.g. colestyramine): Absorption of thiazide diuretics is decreased by anion exchange resins e.g. colestyramine. A decrease of the pharmacological effect may be expected.

Vitamin D: Use of thiazide diuretics may decrease urinary excretion of calcium, and co-administration of Vitamin D may potentiate the increase in serum calcium.

Ciclosporin: Concomitant treatment with diuretics may increase the risk of hyperuricaemia and gout-type complications.

Calcium salts: Concomitant use of thiazide-type diuretics may cause hypercalcaemia by increasing tubular calcium reabsorption. The resulting hypercalcaemia may persist and be symptomatic in patients with hyperparathyroidism (weakness, fatigue, anorexia).

Diazoxide: Thiazide diuretics may enhance the hyperglycaemic effect of diazoxide.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No data available.

Use in pregnancy (Category C)
Category C: "Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible."

Hygroton 25, 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 medicines must not be used to treat hypertension in pregnant women. The use of Hygroton 25 for other indications (e.g. heart disease) in pregnancy should be avoided unless there are no safer alternatives.

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia, foetal bone marrow depression and foetal and neonatal jaundice have been reported with thiazides and related diuretics. During the latter part of pregnancy, products of this type should therefore only be given on sound indications, and then in the lowest effective dose.

Teratogenicity studies in rats and rabbits revealed no teratogenic potential at oral doses up to 1000 and 300 mg/kg/day, respectively.

Use in lactation
Chlortalidone passes into breast milk. For safety reasons, avoid use in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Hygroton 25, especially at the start of treatment, may impair the patient's reactions, e.g. when driving or operating machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse drug reactions which have been derived from multiple sources, including post-marketing experience with Hygroton 25 are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first.
Frequency estimate: very rare < 1/10,000; rare ≥ 1/10,000 to < 1/1,000; uncommon ≥ 1/1,000 to < 1/100; common ≥ 1/100 to < 1/10; very common ≥ 1/10, Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: thrombocytopaenia, leucopaenia, agranulocytosis, eosinophilia

Immune system disorders
Hypersensitivity

Metabolism and nutritional disorders
Very common: (mainly at higher doses) hypokalaemia, hyperuricaemia, hyperlipidemia
Common: hyponatraemia, hypomagnesaemia, hyperglycaemia, decreased appetite
Rare: hypercalcaemia, diabetes mellitus inadequate control, gout
Very rare: hypochloraemic alkalosis

Nervous system disorders
Common: dizziness
Rare: paraesthesia, headache

Ear and labyrinth disorders
Vertigo

Eye disorders
Rare: visual impairment
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-like diuretics.)

Respiratory, thoracic and mediastinal disorders
Very rare: non cardiogenic pulmonary oedema

Gastrointestinal disorders
Common: abdominal discomfort
Rare: mild nausea and vomiting, abdominal pain upper, constipation, diarrhoea
Very rare: pancreatitis

Hepatobiliary disorders
Rare: intrahepatic cholestasis, jaundice

Skin and subcutaneous disorders
Common: urticarial, other forms of skin rash
Rare: photosensitivity reaction

Musculoskeletal and connective tissue disorders
Common: muscular weakness

Renal and urinary disorders
Rare: glycosuria
Very rare: tubulointerstitial nephritis

Cardiac disorders
Rare: arrhythmia

Vascular disorders
Common: orthostatic hypotension which may be aggravated by alcohol, anaesthetics or sedatives
Very rare: vasculitis

Reproductive system and breast disorders
Common: erectile dysfunction

Investigations
Very rare: blood cholesterol increased

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and symptoms
In poisoning due to an overdosage the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Management
Induction of vomiting or gastric lavage and administration of activated charcoal. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Intravenous fluid and electrolyte replacement may be indicated.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Chlortalidone, the active substance of Hygroton 25 is a sulfonamide-derived 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 collecting 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 as little as 12.5 mg Hygroton 25. 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, blunting antihypertensive efficacy.

In hypertensive individuals, chlortalidone 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 slightly below normal and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of Hygroton 25 is dose-dependent between 12.5 and 50 mg/day. Raising the dose above 50 mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when Hygroton 25 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 especially well to diuretics as primary therapy.
Combined treatment with other antihypertensives potentiates the blood pressure lowering effects. In a large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

Because thiazide diuretics including chlortalidone reduce Ca++ excretion, they have been used to prevent the formation of recurrent renal calcium oxalate stones.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
The bioavailability of an oral dose of 50 mg Hygroton 25 is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50 mg, C_{max} values average 1.5 microgram/mL (4.4 micromol/L) and 3.2 microgram/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, steady-state blood concentrations, measured at the end of the 24-hour dosage interval, averaging 7.2 microgram/mL (21.2 micromol/L) are reached after 1 to 2 weeks.

Distribution
In blood, only a small fraction of chlortalidone 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 chlortalidone in whole blood was found in plasma at steady state during treatment with 50 mg doses. *In vitro*, plasma protein binding of chlortalidone is about 76%, and the major binding protein is albumin.

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

Metabolism and Excretion
Chlortalidone is eliminated from whole blood and plasma 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 chlortalidone is excreted by the kidneys, with a mean renal plasma clearance of 60 mL/min. 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.

Special patient groups
Renal dysfunction does not seem to alter the pharmacokinetics of chlortalidone, the rate-limiting factor in the elimination of the medicine from blood or plasma being most probably the affinity of the medicine to the carbonic anhydrase of erythrocytes.

In elderly patients, the elimination of chlortalidone 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 Hygroton 25.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Tests for induction of gene mutations in bacteria or cultured mammalian cells were negative. At high cytotoxic doses, chromosome aberrations were induced in Chinese hamster ovary (CHO) cells. However, a test for unscheduled DNA synthesis in rat hepatocytes showed no evidence for the ability to induce DNA damage, and *in vivo* tests for micronuclei in mouse bone marrow and rat liver revealed no evidence for the induction of chromosome damage. Thus, the results in the CHO cell assay are considered an artefact arising from cytotoxicity, rather than a reflection of genotoxicity. It is concluded that chlortalidone does not present a risk of mutagenicity to humans.

Carcinogenicity
Long-term carcinogenicity studies have not been performed with chlortalidone.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hygroton contains colloidal anhydrous silica, lactose monohydrate, magnesium stearate, maize starch, purified talc, iron oxide yellow and iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Hygroton is supplied in glass bottles of 50 tablets.

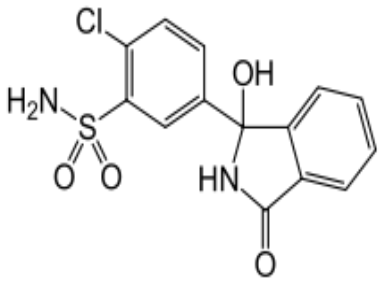
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chlortalidone



Chemical formula: 2-chloro-5-(1-hydroxy-3-oxo-1,2-dihydroisoindol-1-yl)-benzenesulfonamide

Molecular formula: $C_{14}H_{11}ClN_2O_4S$
Molecular weight: 338.767

Chlortalidone is a white or creamy-white odourless, or almost odourless, tasteless crystalline powder. Melting point is about 220°C with decomposition. Chlortalidone is practically insoluble in water; soluble 1 in 150 parts of alcohol, 1 in 650 parts of chloroform, and 1 in 25 parts of methyl alcohol; slightly soluble in ether; soluble in solutions of alkali hydroxides.

CAS number
77-36-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

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Ph: 1800 627 680

9 DATE OF FIRST APPROVAL

02 August 1991

10 DATE OF REVISION

07 September 2021

Amdipharm Mercury (Australia) Pty Ltd is licensed to use the trademark Hygroton.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of warning in association with choroidal effusion
4.8	Addition of choroidal effusion as an adverse event