

NEW ZEALAND DATA SHEET

1 HYGROTON

Chlorthalidone 25 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25mg chlorthalidone

3 PHARMACEUTICAL FORM

Hygroton 25 mg tablets are speckled pale orange, round, approximately 7.1 mm diameter, flat tablets with bevelled edges. The tablets are imprinted CW and a scoreline on one side and nothing on the other side. Each tablet contains 25 mg of chlorthalidone.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Arterial hypertension, essential or nephrogenic or isolated systolic, as primary therapy or in combination with other antihypertensive agents.
- Stable, chronic heart failure of mild to moderate degree (New York Heart Association, NYHA: functional class II or III).
- Oedema of specific origin.
- Oedema due to peripheral (chronic) venous insufficiency; short-term therapy if physical measures prove insufficient.
- Fluid retention in premenstrual syndrome only if the gain in weight is the main symptom and is well documented.
- Ascites due to cirrhosis of the liver in stable patients under close control.
- Oedema due to nephrotic syndrome.
- Prophylaxis against recurrent calcium oxalate calculi in patients with idiopathic, normocalcaemic hypercalciuria.

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 is recommended, either daily or every other day, to be taken in the morning with food.

Hypertension

The range of clinically useful doses is 12.5-50 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 3-4 weeks. If the decrease in blood pressure proves inadequate with 25 or 50 mg/day, combined treatment

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with other antihypertensive drugs, such as β -blockers, reserpine, and ACE inhibitors (see section 4.4), is recommended.

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

The recommended starting dose is 25-50 mg/day. In severe cases, it may be increased up to 100-200 mg/day. The usual maintenance dose is the lowest effective dose, e.g. 25-50 mg either daily or every other day. If the response proves inadequate, digitalis or an ACE inhibitor or both, may be added (see section 4.4).

Oedema of specific origin

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

Prophylaxis against recurrent calcium oxalate calculi in normocalcaemic hypercalciuria

In most cases the optimum prophylactic dose is 25 mg/day. Efficacy is not enhanced by doses higher than 50 mg/day.

Children

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

Elderly patients and patients with renal impairment

The standard lowest effective dose of Hygroton is recommended for patients with mild renal insufficiency and for elderly patients. 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.

Hygroton and thiazide diuretics lose their diuretic effect when the creatinine clearance is <30 mL/min.

4.3 Contraindications

- Anuria, severe renal failure (creatinine clearance lower than 30 mL/min), and severe hepatic failure.
- Hypersensitivity to chlorthalidone and other sulphonamide derivatives or to any of the excipients.
- Refractory hypokalaemia or conditions involving enhanced potassium loss, hyponatraemia and hypercalcaemia.
- Symptomatic hyperuricaemia (history of gout or uric acid calculi).
- Hypertension during pregnancy.

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4.4 Special warnings and precautions for use

Hygroton should be used with caution in patients with impaired hepatic function or progressive liver disease since minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma, especially in patients with liver cirrhosis (see section 4.3).

Electrolytes

Treatment with thiazide diuretics has been associated with electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hypercalcaemia, and hyponatraemia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided.

Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaliuresis induced by Hygroton is dose dependent and varies in extent from one subject to another. With 25-50 mg/day, the decrease in serum potassium concentrations averages 0.5 mmol/L. Periodic serum electrolyte determinations should be carried out especially in digitalised patients. For chronic treatment, serum potassium concentrations should be monitored at the start of therapy and then after 3-4 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 4-6 months.

If necessary, Hygroton may be combined with oral potassium supplements or a potassium-sparing diuretic (e.g. triamterene). In cases of combined treatment, serum potassium should be monitored. If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis and ECG alteration), Hygroton should be discontinued.

Combined treatment consisting of Hygroton and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.

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 as there have been isolated reports of hyponatraemia with neurological symptoms e.g. nausea, debility, progressive disorientation and apathy following thiazide treatment.

For nephrotic syndrome, Hygroton should be used only under close control in normokalaemic patients with no signs of volume depletion.

Elderly patients are more sensitive to hypotensive and electrolyte effects, with potassium loss and the consequent risk of digitalis toxicity. Furthermore, in elderly patients, the potent, long-lasting diuretic effect of chlorthalidone may cause clear urinary incontinence.

Metabolic effects

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

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Although glucose tolerance may be adversely affected, diabetes mellitus very seldom occurs under long-term 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 treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for debate.

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

Other effects

The antihypertensive effect of ACE inhibitors or angiotensin II receptor blockers is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2-3 days and/or that the ACE inhibitor or angiotensin II receptor blockers therapy be started with a low initial dose of the ACE inhibitor or angiotensin II receptor blockers.

Photosensitivity

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Hygroton may be combined with all medicinal products used for the treatment of hypertension, the action of which is potentiated by Hygroton. It can also be combined with medicinal products used for the treatment of heart failure.

The administration of chlorthalidone may affect the action of the following drugs:

Diuretics may reduce lithium excretion and thus increase its plasma levels. Since diuretics raise blood lithium levels, the latter must be monitored in patients under lithium therapy who are taking Hygroton at the same time. Where lithium has induced polyuria, diuretics may exert a paradoxical antidiuretic effect.

Diuretics potentiate the action of curare derivatives.

Antihypertensive drugs action may be potentiated by diuretics (e.g. guanethidine, methyldopa, β -blockers, vasodilators, calcium antagonists, ACE inhibitors). The combination of diuretics and ACE inhibitors may lead to severe hypotension. It is recommended that the dosage of Hygroton be reduced or administration interrupted 2 to 3 days prior to starting treatment with an ACE inhibitor and/or that this treatment be started with a low dose of the ACE inhibitor.

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It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents due to the risk of reduction of the hypoglycaemic effect, caused by the possible reduction of insulin release by the pancreas due to the hypokalaemic effect.

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis-induced cardiac arrhythmias, (see section 4.4).

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Administration of thiazide diuretics with vitamin D or with calcium salts may potentiate the increase in serum calcium, due to an inhibition of urinary excretion.

The action of chlorthalidone may be affected by the administration of the following drugs: The hypokalaemic effect of diuretics may be increased by corticosteroids, ACTH, β_2 -agonists, amphotericin, and carbenoxolone with risk of heart and/or muscle disorders.

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

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

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as cholestyramine. A decrease in the pharmacological effect may be expected.

Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

By analogy with all the other diuretics, it is noted that there is a decrease in the anticoagulant effect of oral anticoagulants when combined with Hygroton.

Concomitant administration of ketanserin increases the risk of hypokalaemia and a prolonged QT interval.

4.6 Fertility, pregnancy and lactation

Category C

Chlorthalidone is contraindicated for hypertension in pregnancy.

There are no or limited data from the use of chlorthalidone in pregnant women. Hygroton, like other diuretics, can cause placental hypoperfusion. Thiazides and related diuretics enter the foetal circulation and may cause electrolyte disturbance. Neonatal thrombocytopenia, foetal bone marrow depression and foetal and neonatal jaundice has been reported with thiazides and related diuretics.

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Thiazide diuretics may also have a direct effect on the smooth muscle.

Chlorthalidone passes into breast milk at a percentage such that it is expected to have an effect on new-borns/infants. Chlorthalidone is excreted with maternal milk at low amounts (milk: plasma ratio 0.05%). As thiazide diuretics may suppress breast-feeding during the first month, and due to the possible theoretical undesirable effects in infants, its use must be avoided in breastfeeding women.

For safety reasons, avoid use in nursing mothers or breastfeeding should be discontinued during treatment with Hygroton.

Women of childbearing potential

It is not recommended to use chlorthalidone in women of childbearing potential that are not using contraceptive methods, unless the clinical condition of the woman requires treatment with chlorthalidone.

Chlorthalidone crosses the placental barrier. In mothers treated with chlorthalidone 50 mg daily, before and after labour, drug levels in foetal blood were about 15% of those found in maternal blood. The concentrations of chlorthalidone in amniotic fluid were about 4% of maternal blood levels.

4.7 Effects on ability to drive and use machines

Hygroton, especially at the start of treatment, may impair the patient's reactions particularly at the start of treatment. Caution is recommended, observing how treatment affects driving or operating dangerous or poor precision machines as well as performing other activities requiring concentration.

4.8 Undesirable effects

The following adverse drug reactions which have been derived from multiple sources, including post-marketing experience with Hygroton 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. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. Frequency estimate: very rare < 0.01%; rare \geq 0.01% to < 0.1%; uncommon \geq 0.1% to < 1%; common \geq 1% to < 10%; very common \geq 10%, not known: cannot be estimated from the available data.

Blood and lymphatic system disorders

Rare: thrombocytopenia, leukopenia, agranulocytosis, and eosinophilia.

Immune system disorders

Not Known: Hypersensitivity to chlorthalidone, other sulphonamide derivatives or any of the excipients.

Metabolism and nutrition disorders

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and hyperlipidaemia.

Common: hyponatraemia, hypomagnesaemia, hyperglycaemia and decreased appetite.

Rare: hypercalcaemia, worsening of diabetic metabolic state, and gout.

Very rare: alkalosis hypochloraemic, alkalosis hypokalaemic.

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Nervous system disorders

Common: dizziness, vertigo, weakness.

Rare: paraesthesia, headache.

Eye disorders

Rare: disturbances of vision.

Cardiac disorders

Rare: arrhythmia.

Vascular disorders

Common: orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives.

Very rare: vasculitis.

Respiratory, thoracic and mediastinal disorders

Very rare: idiosyncratic/ non-cardiogenic pulmonary oedema.

Gastrointestinal disorders

Common: minor gastrointestinal distress.

Rare: mild nausea and vomiting, abdominal pain upper, constipation, and diarrhoea.

Very rare: pancreatitis.

Hepatobiliary disorders

Rare: cholestasis or jaundice.

Skin and subcutaneous tissue disorders

Common: urticaria and other forms of skin rash.

Rare: photosensitivity reaction.

Renal and urinary disorders

Rare: glycosuria.

Very rare: allergic tubulointerstitial nephritis.

Reproductive system and breast disorders

Common: erectile dysfunction.

Investigations

Very rare: blood cholesterol increased.

Interference with the results of diagnostic tests:

- The concomitant administration of thiazide diuretics during the bentiromide test period will invalidate the results of it as thiazide diuretics are also metabolised to arylamines and therefore will increase the percentage of para amino benzoic acid (PABA) recovered.

And with physiological/laboratory values:

- Bilirubin
- Calcium
- Cholesterol, low-density lipoproteins and triglycerides
- Creatinine (serum concentrations may increase)
- Glucose in blood and urine

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- Magnesium, potassium and sodium
- Protein-bound iodine (serum concentrations may decrease)
- Uric acid
- Calcium concentrations in urine (may decrease)

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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.

Treatment

There is no specific antidote. Induction of vomiting or gastric lavage and administration of activated charcoal should be employed to reduce absorption if the patient is conscious. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated. Supplementation with artificial plasma may be required.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group, ATC Code: Thiazide-type diuretic, C03BA04.

Chlorthalidone, the active substance of Hygroton, is a benzothiadiazine (thiazide)-related diuretic, chemically related to the sulphonamides, 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 12.5 mg Hygroton. 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 2-3 hours, reaches its maximum after 4-24 hours, and may persist for 2-3 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 pre-treatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of Hygroton 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 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 a large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

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Because thiazide diuretics including Hygroton reduce Ca^{++} excretion, they have been used to prevent the formation of recurrent renal calcium oxalate stones. In addition, bone loss in elderly women was reduced.

Thiazide diuretics have been found to be useful in nephrogenic diabetes insipidus. The mechanism of action has not been elucidated.

5.2 Pharmacokinetic properties

Absorption and plasma concentration

The bioavailability of an oral dose of 50 mg Hygroton is approximately 64%, peak blood concentrations being attained after 8-12 hours. For doses of 25 and 50 mg, C_{max} values average 1.5 $\mu\text{g}/\text{mL}$ (4.4 $\mu\text{mol}/\text{L}$) and 3.2 $\mu\text{g}/\text{mL}$ (9.4 $\mu\text{mol}/\text{L}$) 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 $\mu\text{g}/\text{mL}$ (21.2 $\mu\text{mol}/\text{L}$), measured at the end of the 24-hour dosage interval, are reached after 1-2 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

Chlorthalidone 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 chlorthalidone is excreted by the kidneys, with a mean renal plasma clearance of 60 mL/min.

Special patient groups

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.

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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.

5.3 Preclinical safety data

Mutagenicity

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

Carcinogenicity

Long-term carcinogenicity studies have not been performed with chlorthalidone.

Reproductive toxicity

Teratogenicity studies in rats and rabbits revealed no teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicon dioxide
Iron oxide red
Iron oxide yellow
Lactose monohydrate
Magnesium stearate
Maize starch
Purified talc

6.2 Incompatibilities

None known.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store below 30°C. Protect from moisture.
Medicines should be kept out of the reach of children.

6.5 Nature and contents of container

Bottle of 50 tablets

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6.6 Special precautions for disposal

No special precautions

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

AFT Pharmaceuticals Ltd
PO Box 33-0232
Takapuna
Auckland
Email:customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

31/12/1969

10 DATE OF REVISION OF THE TEXT

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SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
November 2018	All	Reformat consistent with new Medsafe Data Sheet Template.