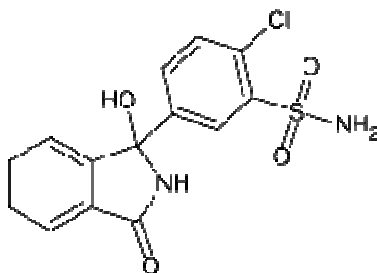


PRODUCT INFORMATION

HYGROTON® (Chlorthalidone Tablets 25 mg)

NAME OF THE MEDICINE

Chlorthalidone



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

Molecular weight - 338.767

CAS number - 77-36-1

DESCRIPTION

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

Excipients: silica colloidal - anhydrous, lactose, magnesium stearate, starch - maize, talc - purified, iron oxide yellow CI77492 and iron oxide red CI77491.

PHARMACOLOGY

Pharmacodynamics

Chlorthalidone, the active substance of Hygroton, 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 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. 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, 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 slightly below normal 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 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 Hygroton reduce Ca^{++} excretion, they have been used to prevent the formation of recurrent renal calcium oxalate stones.

Pharmacokinetics

Absorption and plasma concentration:

The bioavailability of an oral dose of 50 mg Hygroton 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 $\mu\text{g/mL}$ (4.4 $\mu\text{mol/L}$) and 3.2 $\mu\text{g/mL}$ (9.4 $\mu\text{mol/L}$) 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 $\mu\text{g/mL}$ (21.2 $\mu\text{mol/L}$) 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 breast milk. In mothers treated with 50 mg chlorthalidone daily before and after delivery, chlorthalidone levels in fetal 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 and 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. 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 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.

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.

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.

CONTRAINDICATIONS

Anuria, severe renal and hepatic failure. Hypersensitivity to chlorthalidone and other sulphonamide derivatives or to any of the excipients in Hygroton. Refractory hypokalaemia, hyponatraemia and hypercalcaemia. Symptomatic hyperuricaemia (history of gout or uric acid calculi). Hypertension during pregnancy. Creatinine clearance lower than 30 mL/min. Conditions involving enhanced potassium loss, for example, salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function.

PRECAUTIONS

Renal and hepatic impairment:

Hygroton should be used with caution in patients with renal disease or with impaired hepatic function (see "CONTRAINDICATIONS").

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

Hygroton and the 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.

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 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 ACE inhibitor; in patients on high doses of a β -adrenergic agonist; and in all cases where plasma potassium concentrations are <3.0 mmol/L. If oral potassium preparations are not tolerated, Hygroton 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 should be discontinued.

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

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 should be used only under close control in normokalaemic patients with no signs of volume depletion or severe hypoalbuminaemia.

Metabolic effects:

Hygroton 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 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).

Combination with an ACE inhibitor:

The antihypertensive effect of ACE inhibitors is potentiated by 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. 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 be used.

Genotoxicity and carcinogenicity:

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 chlorthalidone does not present a risk of mutagenicity to humans.

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

Use in Pregnancy (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, 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 Hygroton 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 fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has 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

Chlorthalidone passes into breast milk. For safety reasons, avoid use in nursing mothers.

Effects on ability to drive and use machines:

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

Interactions with other drugs

Lithium: 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.

Curare derivatives and antihypertensive drugs: Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyl dopa, beta-blockers, vasodilators, calcium antagonists, ACE inhibitors).

Corticosteroids, ACTH, amphotericin, and carbenoxolone: The hypokalaemic effect of diuretics may be increased by corticosteroids, ACTH, amphotericin, and carbenoxolone.

Insulin and oral antidiabetic agents: It may prove necessary to readapt the dosage of insulin and of oral antidiabetic agents.

Digitalis: Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis-induced cardiac arrhythmias (see "**PRECAUTIONS**").

Non-steroidal anti-inflammatory drugs: 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.

Allopurinol: Coadministration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Coadministration of thiazide diuretics may increase the risk of adverse effects from amantadine.

Antineoplastic agents (e.g. cyclophosphamide, 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 gastro-intestinal motility and stomach-emptying rate.

Cholestyramine: Absorption of thiazide diuretics is decreased by cholestyramine. A decrease of the pharmacological effect may be expected.

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

Cyclosporin: 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.

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

ADVERSE EFFECTS

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%.

Electrolytes and metabolic disorders:

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, rise in blood lipids.

Common: hyponatraemia, hypomagnesaemia, hyperglycaemia.

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

Very rare: hypochloraemic alkalosis.

Skin:

Common: urticaria, other forms of skin rash.

Rare: photosensitisation.

Liver:

Rare: intrahepatic cholestasis, jaundice.

Cardiovascular system:

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

Rare: cardiac arrhythmias.

Central nervous system:

Common: dizziness.

Rare: paraesthesia, headache.

Gastro-intestinal tract:

Common: loss of appetite, minor gastro-intestinal distress.

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

Very rare: pancreatitis.

Blood:

Rare: thrombocytopenia, leucopenia, agranulocytosis, eosinophilia.

Other:

Common: impotence.

Rare: disturbances of vision.

Very rare: idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis, vasculitis.

DOSAGE AND 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 drugs (such as beta-blockers and ACE inhibitors) is recommended. When adding an ACE inhibitor, Hygroton should be reduced or discontinued (see "**PRECAUTIONS**").

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 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 drug (e.g. digitalis), possibly combined with an ACE inhibitor, may be added. In the latter case, Hygroton is to be reduced or discontinued (see "**PRECAUTIONS**").

Oedema of specific origin (see "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.

OVERDOSAGE

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. Intravenous fluid and electrolyte replacement may be indicated.

Safety note concerning children: Medicines should be kept out of the reach of children.

PRESENTATION AND STORAGE CONDITIONS

Tablet, 25 mg (Pale orange, speckled, round, flat tablets with bevelled edges. One side carries the imprint "CG", the other "C/W" and a score.): 50's.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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AFT Pharmaceuticals Ltd,
Auckland, New Zealand
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POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF APPROVAL

Date of TGA approval

19 November 1996

Date of recent amendment

18 March 2009

Version 01