SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hylaton 12.5 mg Tablets

Chlortalidone 12.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hylaton / Chlortalidone Tablets contain 12.5 mg of chlortalidone per tablet.

Excipient(s) with known effect

Each tablet contains 39.09 mg of lactose monohydrate. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, circular and convex tablets without break line, with a diameter of 5.0 ± 0.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of arterial hypertension, essential or nephrogenic or isolated systolic.

Treatment of stable, chronic heart failure of mild to moderate degree (New York Heart Association, NYHA: functional class II or III)

Oedema of specific origin

Ascites due to cirrhosis of the liver in stable patients under close control. Oedema due to nephrotic syndrome.

Diabetes Insipidus.

4.2 Posology and method of administration

Posology

The dosage of Hylaton / Chlortalidone Tablets should be individually titrated to give the lowest effective dose; this is particularly important in the elderly.

Chlortalidone should be taken orally, preferably as a single daily dose at breakfast time.

Adults:

Hypertension

The recommended starting dose is 25mg/day. This is sufficient to produce the maximum hypotensive effect in most patients. If the decrease in blood pressure proves inadequate with 25mg/day, then the dose can be increased to 50mg/day.

If a further reduction in blood pressure is required, additional hypertensive therapy may be added to the dosage regime.

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

The recommended starting dose is 25 to 50mg/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/day 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 “Special warnings and precautions for use”).

Oedema of specific origin (see Section 4.1 “Therapeutic indications”)

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

Diabetes insipidus

Initially 100 mg twice daily but reducing where possible to a daily maintenance dose of 50 mg.

Paediatric population

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

Elderly patients and patients with renal impairment:

The lowest effective dose of Hylaton /Chlortalidone Tablets is also recommended for patients with mild renal insufficiency and for elderly patients (see Section 5.2 “Pharmacokinetic properties”).

In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, a reduction in the recommended adult dosage may be needed. Close medical observation is indicated when treating patients of advanced age with chlortalidone.

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

4.3 Contraindications

Known hypersensitivity to chlortalidone or any of the excipients. Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min), hypersensitivity to chlortalidone and other sulphonamide derivatives, refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic, hyperuricaemia (history of gout or uric acid calculi), hypertension during pregnancy, untreated Addison’s disease and concomitant lithium therapy.

4.4 Special warnings and precautions for use

Warnings:

Hylaton / Chlortalidone Tablets 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 “Contra-indications”).

Chlortalidone should also be used with caution in patients with severe renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated administration may be cumulative.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, 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 drug intake 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.

Precautions:

Electrolytes:

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

Hypokalaemia may increase the excitability of the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaluresis induced by chlortalidone is dose dependent and varies in extent from one subject to another. With 25 to 50 mg/day, the decrease in serum potassium concentrations averages 0.5mmol/l.

Periodic serum electrolyte determinations should be carried out, particularly in digitalised patients.

If necessary, Hylaton / Chlortalidone Tablets may be combined with oral potassium supplements or with a potassium- sparing diuretic (e.g. triamterene).

If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis and ECG alteration), Hylaton / Chlortalidone Tablets should be discontinued.

Combined treatment consisting of Hylaton / Chlortalidone Tablets and a potassium salt or a potassium-sparing diuretic should be avoided in patients treated with 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. There have been isolated reports of hyponatraemia with neurological symptoms (e.g. nausea, debility, progressive disorientation and apathy) following thiazide treatment.

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

Metabolic effects:

Chlortalidone may raise the serum uric acid level, but attacks of gout are uncommon during chronic treatment.

As with the use of other thiazide diuretics, glucose intolerance may occur; this is manifest as hyperglycaemia and glycosuria. Chlortalidone may very seldom aggravate or precipitate diabetes mellitus; this is usually reversible on stopping therapy.

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.

Hylaton / Chlortalidone Tablets 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).

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Other effects:

The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.

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

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).

The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, ß2 – agonists, amphotericin and carbenoxolone.

It may prove necessary to adjust the dosage of insulin and oral anti-diabetic agents.

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

Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indometacin) may reduce the diuretic and antihypertensive activity of chlortalidone; 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 colestyramine. A decrease in the pharmacological effect may be expected.

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.

The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcaemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.

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

Thiazide and related diuretics can cause a rapid rise in serum lithium levels as the renal clearance of lithium is reduced by these compounds.

4.6 Fertility, pregnancy and lactation

Pregnancy

Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics.

Breastfeeding

Chlortalidone passes into the breast milk; mothers taking chlortalidone should refrain from breast-feeding their infants.

4.7 Effects on ability to drive and use machines

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

4.8 Undesirable effects

Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%; uncommon ≤0.1%

to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders:
Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.
Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.
Uncommon: gout.
Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.
Very rare: hypochloraemic alkalosis.

Skin:
Common: urticaria and other forms of skin rash.
Rare: photosensitisation.

Liver
Rare: intrahepatic cholestasis or jaundice.

Cardiovascular system:
Common: postural hypotension.
Rare: cardiac arrhythmias.

Central nervous system:
Common: Dizziness.
Rare: paraesthesia, headache.

Gastro-intestinal tract;
Common: loss of appetite and minor gastrointestinal distress.
Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.
Very rare: pancreatitis.

Blood:
Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.

Eye disorders:
Frequecncy unknown: choroidal effusion

Other effects:
Common: impotence
Rare: Idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Treatment
There is no specific antidote to chlortalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken Intravenous fluid and electrolyte replacement may be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C03BA04

Chlortalidone 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 chlortalidone. 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, 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 somewhat reduced and plasma renin activity may be elevated.

On chronic administration, the antihypertensive effect of chlortalidone 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 chlortalidone 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 chlortalidone, 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, chlortalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated. 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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of an oral dose of 50 mg chlortalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50 mg, Cmax values average 1.5 μg/ml (4.4 μmol/L) and 3.2μg/ml (9.4 μmol/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 7.2μg/ml (21.2 μmol/L), measured at the end of the 24 hour dosage interval, 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 the 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

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 the faeces, mainly in unchanged form.

Elimination

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 clearance of 60 ml/min.

Renal impairment

Renal dysfunction does not alter the pharmacokinetics of chlortalidone, 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.

Elderly patients

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 chlortalidone.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline

Lactose monohydrate

Povidone

Sodium starch glycolate (Type A)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Tablets are packed in blister PVC/PVdC and aluminium.

Hylaton / Chlortalidone Tablets are supplied in blister packs of 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0351

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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