1. NAME OF THE MEDICINAL PRODUCT

[Hydrochlorothiazide 25mg Tablets]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 25 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antihypertensive/diuretic

Arterial hypertension; as monotherapy or in combination with other antihypertensive agents

Stable, chronic heart failure of mild to moderate degree (New York Heart Association - NYHA - classes II and III)

Oedema of specific origin:
- oedema due to peripheral (chronic) venous insufficiency; short-term therapy if physical measures prove insufficient
- ascites due to cirrhosis of the liver in stable patients under close control

Prophylaxis of recurrent calcium oxalate calculi in patients with idiopathic, normocalcemic, hypercalciuria

Nephrogenic diabetes insipidus

4.2 Posology and method of administration

Dosage
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. The daily dosage of hydrochlorothiazide can be administered as a single dose or in two divided doses. It can be taken with or without food.

General target population
Hypertension
The clinically useful dosage range is 12.5-50 mg/day. The recommended starting doses are either 12.5 or 25 mg/day. 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 with other antihypertensive drugs is recommended.

Sodium and/or volume depletion should be corrected prior to the use of hydrochlorothiazide in combination with an ACE inhibitor or an angiotensin receptor blocker (ARB), or a direct renin inhibitor (DRI), or the treatment should start under close medical supervision.

Stable, chronic heart failure (NYHA class II/III)
The recommended starting doses are 25-50 mg/day. In patients with severe chronic heart failure (NYHA class IV), who cannot tolerate loop diuretics, initial doses of 75 mg hydrochlorothiazide daily may be given. Sodium and/or volume depletion should be corrected before using hydrochlorothiazide in combination with an ACE inhibitor, or an angiotensin receptor blocker (ARB). Otherwise, treatment should start under close medical supervision.

Edema of specific origin
The lowest effective dose should be identified by titration and administered over limited periods only. Doses should not exceed 50 mg/day.

Prophylaxis of recurrent calcium oxalate calculi in normocalcemic hypercalciuria
The recommended daily doses are 25-50 mg.

Nephrogenic diabetes insipidus (NDI)
The recommended dose in children with NDI is 1-2 mg/kg/day while carefully monitoring blood potassium levels. In adults, initial doses of up to 100 mg have been used.

Special populations
Renal impairment
Patients with mild to moderate renal impairment require no adjustment of the initial dose (see section 5.2). Use with caution in patients with severe renal disease (GFR < 30 mL/min) (see section 4.4). Hydrochlorothiazide and other thiazide diuretics may lose their diuretic effect when the GFR is < 30 mL/min but may be useful in these patients, when used with due caution in combination with a loop diuretic. Hydrochlorothiazide is contraindicated in patients with anuria (see section 4.3).

Hepatic impairment
Patients with mild to moderate hepatic impairment require no adjustment of the initial dose (see section 5.2). Thiazides, like other diuretics, may precipitate electrolyte imbalance, hepatic encephalopathy and hepato-renal syndrome, when used to treat cirrhotic ascites. Hydrochlorothiazide should be used with particular caution in patients with severe hepatic impairment (see section 4.4).

Method of administration
Oral formulation

4.3 Contraindications

- Known hypersensitivity to hydrochlorothiazide, other sulfonamide derivatives or to any of the excipients
- Anuria
- Hypertension during pregnancy

4.4 Special warnings and precautions for use

Renal impairment
Use with caution in severe kidney disease (GFR < 30 mL/min). Thiazide diuretics may precipitate azotemia in patients with chronic kidney disease. They are ineffective as monotherapy in severe kidney disease (GFR < 30 mL/min) but may be useful, when used with due caution in combination with loop diuretics even in patients with GFR < 30ml/min (see sections 4.2 and 5.2).

Hepatic impairment
Patients with mild or moderate hepatic impairment require no adjustment of the initial dose (see sections 4.2 and 5.2). Thiazides, like other diuretics, may precipitate electrolyte imbalance, hepatic encephalopathy and hepato-renal syndrome when used to treat cirrhotic ascites. Hydrochlorothiazide should be used with particular caution in patients with severe hepatic impairment.

Electrolytes
Thiazide diuretics may precipitate new-onset hypokalemia or exacerbate pre-existing hypokalemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. Correction of hypokalemia and any coexisting hypomagnesaemia is recommended prior to the initiation of thiazides. Potassium and magnesium serum concentrations

should be checked periodically. All patients receiving thiazide diuretics should be monitored for imbalances in electrolyte particularly potassium.

As with all thiazide diuretics, kaluresis induced by hydrochlorothiazide is dose dependent. For chronic treatment, serum potassium concentrations should be checked initially and then after 3-4 weeks. Thereafter - if the potassium balance is not disturbed by additional factors (e.g. vomiting, diarrhea, change in renal function, etc.) - checks should be carried out periodically.

Titrated co-administration of an oral potassium salt (e.g. KCl) may be considered in patients receiving digitalis (see section 4.5); 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, hydrochlorothiazide may be combined with a potassium-sparing diuretic.

In all cases of combined treatment, maintenance or normalization of the potassium balance should be checked closely. If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alteration), hydrochlorothiazide should be discontinued.

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

Thiazide diuretics can precipitate new onset hyponatremia or exacerbate pre-existing hyponatremia. In severely sodium depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of treatment with hydrochlorothiazide. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases.

Thiazide diuretics should be used only after correction of any pre-existing sodium and/or volume depletion. Otherwise, the treatment should start under close medical supervision. Regular monitoring of serum sodium concentrations is recommended.

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

Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Metabolic effects
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, it should be used with caution in patients with hypercalcemia. Marked hypercalcemia unresponsive to thiazide withdrawal or ≥ 12 mg/dL may be evidence of an underlying thiazide independent hypercalcemic process. Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary.

Acute myopia and secondary angle-closure glaucoma
Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in 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 hydrochlorothiazide 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 sulfonamides or penicillin allergy.

Others
The antihypertensive effect of ACE inhibitors, ARBs or DRIs is potentiated by agents that increase plasma renin activity (diuretics). Caution should be exercised when an ACE inhibitor (or ARB or DRI) is added to hydrochlorothiazide particularly in severely sodium-depleted and/or volume depleted patients.

Lupus erythematosus may possibly become activated under treatment with thiazides.

Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

4.5 Interaction with other medicinal products and other forms of interaction

Upon concomitant administration the following drugs may interact with hydrochlorothiazide.

Lithium
Since diuretics raise blood lithium levels, the latter must be monitored in patients under lithium therapy receiving concomitant hydrochlorothiazide. Where lithium has induced polyuria, diuretics may exert a paradoxical antidiuretic effect.

Other antihypertensive drugs
Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and DRIs).

Skeletal muscle relaxants
Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Drugs affecting serum potassium levels
Co-administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics may increase the hypokalemic effect (see section 4.4).

Drugs affecting serum sodium level
Co-administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc., may intensify the hyponatremic effect of diuretics. Caution is advised in long-term administration of these drugs (see also section 4.4).

Antidiabetic agents
It may be necessary to adjust the dosage of insulin and of oral antidiabetic agents.

Digitalis glycosides
Thiazide-induced hypokalemia or hypomagnesemia possibly occurring as unwanted effects may favor the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

NSAIDs and Cox-2 selective agents
Co-administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of hydrochlorothiazide. Concurrent hypovolemia may induce acute renal failure.

Allopurinol

Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine
Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine.

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

Anticholinergic agents
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility. Conversely prokinetic drugs such as cisapride may decrease the bioavailability of thiazide-type diuretics.

Ion exchange resins
Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 h before or 4-6 h after the administration of resins would potentially minimize the interaction.

Vitamin D
Concomitant 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 hyperuricemia and gout-type complications.

Calcium salts
Concomitant use of thiazide-type diuretics may lead to hypercalcemia by increasing tubular calcium reabsorption.

Diazoxide
Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.

Methyldopa
There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Alcohol, barbiturates or narcotics
Co-administration of thiazide diuretics with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.

Pressor amines
Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline but the clinical significance of this effect is not sufficient to preclude their use.

4.6 Pregnancy and lactation

Women of child-bearing potential (WOCBP)
If pregnancy is confirmed in a woman taking hydrochlorothiazide, the treating physician should carefully evaluate the risk and benefit associated with the therapy (see Pregnancy subsection below and section 4.3).

Pregnancy
Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. Thiazides can cross the placenta and their use during pregnancy is associated with a risk of fetal or neonatal jaundice or

thrombocytopenia. 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 hydrochlorothiazide for other indications (e.g. heart disease) in pregnancy should be avoided.

Breast-feeding
Hydrochlorothiazide is excreted into breast milk and may suppress lactation. Avoid use in breast-feeding mothers.
Fertility
There are no human fertility data for hydrochlorothiazide. In animal studies hydrochlorothiazide had no effect on fertility and conception (see section 5.3).

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Adverse reactions are ranked by heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), including isolated reports.

Blood and lymphatic system disorders
Rare: Thrombocytopenia sometimes with purpura
Very rare: Leucopenia, agranulocytosis, bone marrow failure and hemolytic anaemia

Immune system disorders
Very rare: Vasculitis necrotizing, hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary oedema

Metabolism and nutrition disorders
Very common: Mainly at higher doses, hypokalaemia, blood lipids increased
Common: Hyponatraemia, hypomagnesaemia and hyperuricaemia, decreased appetite
Rare: Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state
Very rare: Alkalosis hypochloraemic

Psychiatric disorders
Rare: Sleep disorders

Nervous system disorders
Rare: Headache, dizziness, depression and paresthesia

Eye disorders
Rare: Visual impairment particularly in the first few weeks of treatment

Cardiac disorders
Rare: Arrhythmias

Vascular disorders
Common: Orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives

Gastrointestinal disorders
Common: Mild nausea and vomiting
Rare: Abdominal discomfort, constipation and diarrhea
Very rare: Pancreatitis

Hepatobiliary disorders
Rare: Cholestasis or jaundice

Skin and subcutaneous tissue disorders
Common: Urticaria and other forms of rash
Rare: Photosensitivity reaction
Very rare: Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

Reproductive system and breast disorders
Common: Erectile dysfunction

Adverse drug reactions from post-marketing experiences (frequency not known)
The following adverse drug reactions have been identified based on post-marketing experiences. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequencies.

Blood and lymphatic disorders
Aplastic anemia

Eye disorders
Angle-closure glaucoma

Skin and subcutaneous tissue disorders
Erythema multiforme

Musculoskeletal and connective tissue disorders
Muscle spasm

Renal and urinary disorders
Acute renal failure, renal disorder

General disorders and administration site conditions
Pyrexia, asthenia

4.9 Overdose

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

Management
General supportive measures should be applied in all cases of overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic.

Thiazide diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting NaCl reabsorption (by antagonizing 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 hydrochlorothiazide. The resulting increase in urinary excretion of sodium and chloride, and the less prominent increase in kaluresis are dose dependent. The diuretic and natriuretic effect appears within 1-2 hours after oral administration of hydrochlorothiazide, reaches its maximum after 4-6 hours, and may persist for 10-12 hours.

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. On continued administration, the hypotensive effect is maintained, probably due to a fall in total peripheral vascular 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 hydrochlorothiazide is dose dependent from 12.5 mg up to 50-75 mg/day. The maximum hypotensive effect is reached with 50 mg/day in most patients.

Daily doses above 50 mg may in rare cases enhance the therapeutic benefit, but increase the risk of metabolic side effects.

As with other diuretics, when hydrochlorothiazide is given as monotherapy, blood pressure control is achieved in about 40-50% 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 hydrochlorothiazide reduce Ca++ excretion, they have been used to prevent the formation of recurrent renal calcium oxalate stones.

During long-term treatment, thiazide recipients exhibit a significantly higher mineral content of bones than non-recipients. Accordingly, chronic use of thiazides in elderly people has been shown to be associated with a relevant reduction in the risk of hip fracture, and therefore to significantly reduce this clinically relevant complication of osteoporosis.

In nephrogenic diabetes insipidus, hydrochlorothiazide reduces urinary volume and increases the osmolality of the urine.

6. Pharmacokinetic properties

Absorption
The absorption of hydrochlorothiazide, when administered as hydrochlorothiazide tablets, totals about 70% of the dose. Variations in the absorption as a result of fasting or food intake are of little clinical significance. In patients suffering from congestive heart failure absorption of hydrochlorothiazide is diminished.

After oral administration of single doses of 12.5, 25, 50 and 75 mg, mean peak plasma levels of 70, 142, 260 and 376 ng/mL, respectively, were reached after an average of 2 hours. Within the therapeutic dose range, the systemic availability of hydrochlorothiazide is dose proportional.

Continuous administration does not change the fate of hydrochlorothiazide in the body. After 3 months of treatment with 50 mg hydrochlorothiazide daily, no difference in the absorption, elimination or excretion were detected as compared to shorter-term treatment. During repeated administration of 75 mg hydrochlorothiazide, e.g. daily for 6 weeks, mean steady-state plasma concentrations (Caverage)of 111 ng/mL were observed.

Distribution
Hydrochlorothiazide accumulates in erythrocytes, reaching a peak concentration at about 4 hours after oral administration. After 10 hours, the concentration in erythrocytes is approximately 3 times higher than in plasma. Binding to plasma proteins to the extent of approximately 40-70% has been reported, and the apparent volume of distribution has been estimated at 4-8 L/kg.

Hydrochlorothiazide crosses the placental barrier and reaches levels in the umbilical vein that approach those in maternal plasma. The drug accumulates in the amniotic fluid, exceeding the concentration in umbilical cord vein plasma by a factor of up to 19. Hydrochlorothiazide is excreted

in the breast milk. In the case of a daily intake of approximately 600 mL milk, the infant ingests not more than 0.05 mg of the drug.

Metabolism and elimination
Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. Within 72 hours, 60-80% of a single oral dose is excreted in the urine, 95% in unchanged form, and about 4% as the hydrolysate 2-amino-4-chloro-m-benzenedisulfonamide (ACBS). Up to 24% of an oral dose may be found in the feces, and a negligible amount is excreted via the bile.

Special populations
Geriatric patients
In the elderly, steady-state concentrations of hydrochlorothiazide are higher and systemic clearance is significantly lower than in younger subjects.

Renal impairment
In the presence of renal dysfunction, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, the mean elimination half-life is almost doubled. The renal clearance of hydrochlorothiazide is also reduced to a great extent compared with the renal clearance of around 300 mL/min in patients with normal renal function.

Hepatic impairment
Liver disease does not significantly alter the pharmacokinetics of hydrochlorothiazide and usually no dosage reduction is necessary.

6.1 Preclinical safety data

The mutagenic potential was assessed in a series of in vitro and in vivo test systems. While some positive results were obtained in vitro all in vivo studies provided negative results. It has therefore been concluded that there is no relevant mutagenic potential in vivo.

According to the experimental data available, hydrochlorothiazide revealed no evidence of carcinogenic activity in rats and mice (hepatocellular tumors in mice were only seen in high-dosed males; however, this incidence did not exceed levels historically found in controls).

Hydrochlorothiazide was not teratogenic and had no effects on fertility and conception. No teratogenic potential was revealed in 3 animal species tested, given doses that were at least 10 times greater than recommended human doses of ~1 mg/kg. A decrease in weight gain in suckling rat pups was attributed to the high dose (15 times the human dose) and diuretic effects of hydrochlorothiazide, with subsequent effects on milk production (see section 4.6).

7. PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Carboxymethyl starch sodium (type A) (Ph.Eur.)
Microcrystalline cellulose
Lactose monohydrate
Magnesium stearate (Ph.Eur.)
Maize starch
Colloidal silicon dioxide

Advice to diabetics
1 tablet contains less than 0.01 carbohydrate exchange units.

7.2 Incompatibilities

Not applicable

7.3 Shelf-life

3 years

The medicinal products should not be used any more after the expiry date printed on the package.

7.4 Special precautions for storage

Store below 30^0C