Hydrochlorothiazide 25 mg tablets		
Module 1.3	Product Information	Version: 2019-09-30
Module 1.3.1	Summary of Product Characteristics	

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydrochlorothiazide 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydrochlorothiazide 25 mg tablets:

Each tablet contains 25 mg hydrochlorothiazide

Excipient: Lactose monohydrate. Each tablet contains 101 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Hydrochlorothiazide 25 mg tablets:
White, round tablets with a diameter of 8 mm and a one-sided score notch.
The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Arterial hypertension, as a monotherapy or in combination with other antihypertensives agents.
- Oedema of a particular origin:
  - oedema/mild fluid retention as a result of stable, chronic mild to moderate heart failure (functional class II or III);
  - oedema as a result of nephrotic syndrome, only in patients with normal potassium levels and no sign of volume depletion or severe hypoalbuminaemia;
  - ascites as a result of cirrhosis of the liver in stable patients under strict supervision.
- Prophylaxis of recurrent calcium oxalate stones in patients with idiopathic, normocalcaemic hypercalciuria.
- Nephrogenic diabetes insipidus where treatment with antidiuretic hormone is not indicated.

4.2 Posology and method of administration

Posology
As with all diuretics, treatment must be instituted at the lowest possible dose. This dose must be adjusted according to the response of each individual patient. In this way, the maximum therapeutic effect is achieved, while the undesirable effects are kept to a minimum. Administration up to a daily dose of 50 mg is recommended with breakfast in the morning.

Treatment of arterial hypertension

Adults
The clinical useful doses vary from 12.5 to 50 mg a day.
The recommended initial dose is either 12.5 mg a day or 25 mg a day. This dose may be increased to 50 mg/day, as a single dose or two split doses.
At a given dose, the maximum effect is reached after 3-4 weeks.
Experts recommend that if the reduction in the blood pressure proves to be unsatisfactory at a dose of 25 or 50 mg, doses of hydrochlorothiazide should not be increased, as they do not result in a greater reduction in arterial pressure, but instead increase potassium loss; and rather a combination with another antihypertensive (e.g. a beta blocker or an ACE inhibitor) is to be recommended. It is recommended that the administration of diuretics (such as hydrochlorothiazide) be stopped a couple of days prior to the administration of the ACE inhibitor in order to avoid severe hypotension. For dosage adjustment, each product should be administered separately until the appropriate dosage level is reached.

Stable, chronic cardiac insufficiency (functional class II, III)
Adults
The recommended initial dose is 25-50 mg a day. Depending on the effect, it is possible that this dose can be increased to a maximum of 100 mg a day.
For the maintenance therapy, the lowest possible effective dose is to be given.

Treatment of oedema
Adults

Start with 12.5-25 mg/day and establish the lowest possible effective dose by means of titration. The dose may not be more than 50 mg a day.

Treatment of hypercalciuria:
Adults
The recommended daily dose is 25-50 mg.

Treatment of diabetes insipidus
Adults doses of up to 100 mg are used.

Special populations
Elderly:
Use the adult doses, although they may be more sensitive to the effects of hydrochlorothiazide and may need lower doses.

Children and adolescents (< 18 years)
There is no experience in children and adolescents. Therefore, hydrochlorothiazide should not be administered to children and adolescents.

Patients with renal impairment
For patients with renal impairment (creatinine clearance between 30 and 70 ml/min), a 50% dose reduction is recommended. Hydrochlorothiazide is contraindicated in patients with severe renal impairment (i.e. creatinine clearance ≤ 30 ml/min).

Method of administration
For oral administration.

The tablets should be taken whole (not chewed) at breakfast with a sufficient quantity of liquid.

4.3 Contraindications

Hydrochlorothiazide Apotex must not be used in the following cases:
hypersensitivity to hydrochlorothiazide, to other thiazides or sulfonamides or to any of the excipients (see sections 4.4 and 6.1).
- severe renal disease (impaired renal function with oliguria or anuria; creatinine clearance less than 30 ml/min, serum creatinine greater than 1.8 mg/100 ml),
- acute glomerulonephritis,
- Severe hepatic impairment (hepatic coma and hepatic praecoma),
- hypokalaemia,
- hyponatraemia,
- hypovolaemia,
- hypercalcaemia,
- symptomatic hyperuricaemia (patients with gout in the history), gout

4.4 Special warnings and precautions for use

Hydrochlorothiazide is to be used sparingly in patients with renal disease or hepatic impairment.

Hypotension and electrolyte/fluid imbalance:
Symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients, but was more likely in the presence of fluid depletion or electrolyte imbalance. Therefore, periodic determination of serum electrolytes and creatinine should be performed at appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia, and hypochloraemic alkalosis).
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.
Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out a test for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.
Hyponatraemia accompanied by neurological symptoms (nausea, weakness, progressive disorientation and apathy) has been seen in isolated cases.

Potassium
As with all thiazide diuretics, the excretion of potassium which is caused by hydrochlorothiazide is dose related. At a dose of 12.5 mg/day, the decrease in serum potassium concentrations is on average 0.36 mmol/l after a period of treatment of 6 months. In the case of long-term treatment, the serum potassium concentration has to be established at the start of the treatment and then after 3-4 weeks. This is then to be monitored every 4-6 months if the potassium balance is not affected by other factors (e.g. vomiting, diarrhoea and changes in renal function).
The monitoring of serum electrolytes is particularly important in elderly people, patients with ascites as a result of cirrhosis of the liver and patients with oedema as a result of nephrotic syndrome.
Concomitant treatment with an oral potassium salt (e.g. KCl) or with a potassium-sparing diuretic can be considered in patients receiving digitalis, in the case of symptoms of coronary heart disease, in patients receiving high doses of a β-adrenergic agonist and in all cases where plasma concentrations are < 3.0 mmol/l.
In all cases of combined treatment, the maintenance or normalisation of the serum potassium must be closely monitored. If hypokalaemia is accompanied by clinical symptoms (e.g. muscle weakness, paresis and changes in ECG), the administration of hydrochlorothiazide must be stopped.
Combined treatment consisting of hydrochlorothiazide and a potassium salt or a potassium-sparing diuretic is to be avoided in the case of patients who are also receiving an ACE inhibitor.

Metabolic effects
Just like other diuretics, hydrochlorothiazide can increase the serum uric acid content, but new episodes of gout are only rarely seen with long-term use.
Hydrochlorothiazide must not be used as the medicine of first choice for the long-term treatment of patients with manifest diabetes mellitus. Just as with all thiazide diuretics, glucose tolerance can change during chronic therapy, with the effect being smaller at lower

doses. However, diabetes mellitus only rarely occurs during treatment, certainly in the case of patients in whom there are no other predisposing factors. A worsening of the metabolic situation rarely occurs in the case of diabetics.
Small, sometimes reversible increases in the plasma concentrations of total cholesterol, triglycerides or ”low-density lipoprotein” cholesterol have been reported in patients in the course of long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for discussion.
Hydrochlorothiazide is not to be used as the medicine of first choice in the case of patients who are receiving treatment for hypercholesterolaemia (diet combined therapy).
Calcium excretion is reduced by thiazide diuretics. Pathological changes in the adrenal glands have been seen with hypercalcaemia and hypophosphataemia in individual patients who have received thiazides over a long period of time. If hypercalcaemia occurs, further diagnostic tests are necessary. The usual complications of hyperparathyroidism such as renal lithiasis, bone resorption and peptic ulcers have not been observed.

Renal insufficiency
A 50% dose reduction is recommended for patients with renal impairment (creatinine clearance between 30 and 70 ml/min).
Hydrochlorothiazide is ineffective in patients with renal insufficiency (glomerular filtration rate less than 30 ml/min and/or serum creatinine above 1.8 mg/100 ml). It may cause harm to the patient because it may further decrease glomerular filtration rate. Therefore, Hydrchlorothiazide is not recommended in patients with severe renal impairment (i.e. creatinine clearance < 30 ml/min) (see section 4.3).
Periodic monitoring of potassium, creatinine and uric acid serum levels is recommended.

Hepatic insufficiency:
Hydrochlorothiazide induces fluctuations in serum electrolyte concentrations that may cause a loss of electrolyte homeostasis and hepatic coma may occur in susceptible patients. Caution is therefore recommended when hydrochlorothiazide is administered to patients with liver disease.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Other warnings
Where hydrochlorothiazide is administered with other diuretics or antihypertensive agents, additive effects are observed; advantage is taken of this to increase their effectiveness. Orthostatic hypotension can also occur however, so it is necessary to adjust doses appropriately to the needs of each patient

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

Lupus erythematosus can possibly be exacerbated or activated in the course of treatment with thiazides.

Therapy with hydrochlorothiazide should be stopped in the following cases:

- electrolyte disturbances, which are resistant to therapeutic intervention,
- orthostatic hypotension,
- hypersensitivity reactions,
- severe gastrointestinal disorders,
- central nervous disorders,
- pancreatitis,
- blood disturbances (anemia, leukopenia, thrombocytopenia),
- acute cholecystitis,
- vasculitis,
- aggravation of a pre-existing myopia,
- in patients with serum creatinine greater than 1.8 mg/100 ml and creatinine clearance less than 30 ml/min respectively.

This medicine contains lactose. Patients with rare hereditary disorders such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption must not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended:

Medicinal products associated with potassium loss and hypokalaemia, e.g. kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, laxatives, carbenoxolone, amphotericin B, penicillin G sodium, salicylic acid and derivates:
Simultaneous application of hydrochlorothiazide and medicinal products associated with potassium loss and hypokalaemia, e.g. kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, laxatives, carbenoxolone, amphotericin B, penicillin G sodium, salicylic acid and derivates may enhance the potassium-depleting effect. The monitoring of potassium level is advised. Such combinations are therefore not recommended.

Lithium
Concomitant application of hydrochlorothiazide and lithium may lead to diminished lithium elimination and increased cardiotoxic and neurotoxic effects of lithium. Therefore, co-administration of lithium and hydrochlorothiazide should only be allowed under strict medical supervision and

should not be recommended. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Concomitant use requiring caution

Other diuretics, blood pressure lowering drugs, betablockers, nitrates, barbiturates, phenothiazines, tricyclic antidepressives, vasodilators, alcohol:
The antihypertensive efficacy of Hydrochlorothiazide may be intensified by simultaneous application of other diuretics, blood pressure lowering drugs, betablockers, nitrates, barbiturates, phenothiazines, tricyclic antidepressives, vasodilator or alcohol intake.

ACE inhibitors (e.g. captopril, enalapril):
When administered concurrently with ACE inhibitors (e.g. captopril, enalapril) severe first-dose hypotension and deterioration of renal function may develop. Treatment with diuretics should therefore be stopped 2-3 days before starting ACE inhibitor therapy to reduce the risk of first-dose hypotension.

Salicylates and other NSAIDs (e.g. indometacin) including selective COX-2 inhibitors:
Salicylates and other NSAIDs (e.g. indometacin), including selective COX-2 inhibitors, may diminish antihypertensive and diuretic effects of Hydrochlorothiazide. There are single cases of worsening of renal function, especially in patients with poor pre-existing renal function.
Hydrochlorothiazide may intensify the toxic effects of salicylates on the central nervous system.
During simultaneous application of NSAIDs acute renal failure may occur in those patients, who develop hypovolaemia during hydrochlorothiazide therapy.

Cardiac glycosides
If hypokalaemia or hypomagnesaemia occur as an undesirable effect during treatment with diuretics, cardiac arrhythmias can occur in patients who are also treated with digitalis glycosides. It is recommended to monitor electrolytes and correct any imbalance.

Antidiabetic medicinal products (oral agents or insulin):
Thiazide diuretics reduce insulin sensitivity, increasing glucose intolerance and hyperglycaemia. For this reason, hydrochlorothiazide displays interactions with all antidiabetic agents, whether oral or insulin-based, with a corresponding loss of diabetes control. Diabetic patients who begin a treatment with hydrochlorothiazide should therefore monitor their blood glucose levels. It can be necessary to adjust the dose of insulin or oral antidiabetic.

Metformin:
Metformin should be used with caution owing to the risk of lactic acidosis induced by possible functional renal failure associated with hydrochlorothiazide.

Allopurinol
Concomitant administration of thiazide diuretics can increase the risk of hypersensitivity reactions to allopurinol.

Amantadine
Concomitant administration of thiazide diuretics can increase the risk of undesirable effects of amantadine by decreasing its tubular secretion.

Cytostatics (e.g. cyclophosphamide and methotrexate)
Concomitant administration of thiazide diuretics can reduce the renal excretion of cytostatics and increase the myelosuppressive effects.

Skeletal muscle relaxants of the curare-type:
Effects of skeletal muscle relaxants of the curare-type were increased and prolonged. In cases in which [Product name] cannot be stopped before application of curare-type skeletal muscle relaxants, the anaesthetist must be informed.

Anticholinergics (e.g. atropine and biperiden)
The bioavailability of thiazide-like diuretics can be increased by anticholinergics, which is apparent as a result of a reduction in gastrointestinal motility and gastric emptying speed.

Cholestyramine and cholestipol resins
The absorption of thiazide diuretics is reduced by cholestyramine. A reduction in the pharmacological effect can be expected.
Cholestipol can delay or reduce the absorption of concomitantly administered hydrochlorothiazide as it can display a strong affinity for anions other than bile acids.

Medicinal products affected by serum potassium disturbances:
Periodic monitoring of serum potassium and ECG is recommended when hydrochlorothiazide is administered with agents affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes-inducing substances (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes:

- class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- other agents e.g. bepridil, cisapride, diphemanil, erythomycin IV, halofantrin, mizolastine, pentamidine, sparfloxacin, terfenadine, vincamine IV.

Carbamazepine:
Co-administration of hydrochlorothiazide with carbamazepine may decrease serum sodium levels. Therefore, serum sodium levels should be monitored.

Chinidin:
The clearance of chinidin can be reduced when hydrochlorothiazide and chinidin are given concomitantly.

Tetracyclines:
The concomitant administration of hydrochlorothiazide and tetracyclines may cause an increase in serum urea.

Vitamin D
Co-administration of thiazide with vitamin D supplements may increase serum calcium levels due to decreased excretion of calcium.

Cyclosporine
Concomitant treatment with diuretics can increase the risk of hyperuricaemia and gout-like complications.

Calcium salts
Concomitant use of thiazide-like diuretics can result in hypercalcaemia as there is an increase in tubular calcium reabsorption due to decreased urinary excretion.

Betablockers and diazoxide
Thiazide diuretics can increase the hyperglycaemic effect of diazoxide and betablockers.

Methyldopa
In the literature, the occurrence of haemolytic anaemia has been reported with the concomitant use of hydrochlorothiazide and methyldopa.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited experience with the use of hydrochlorothiazide during pregnancy, particularly during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects such as icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-eclampsia, due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in the rare situations where no other treatment could be used.

Lactation
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the production of milk. The use of Hydrochlorothiazide during lactation is not recommended. If Hydrochlorothiazide is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

Particularly at the start of the treatment, hydrochlorothiazide has minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

The adverse events below are classified where appropriate by system organ class and frequency according to the following convention:

Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1,000, <1/100
Rare: ≥1/10,000, <1/1,000
Very rare: <1/10,000

Not known: cannot be estimated from the available data

The following adverse events may occur due to disturbances in the electrolyte- and fluid imbalance:

During long-term continuous therapy electrolyte- and fluid imbalance is commonly reported, especially hypokalaemia, hyponatraemia, in above hypomagnesaemia, hypochloraemia and hypercalcaemia may develop.
In higher doses loss of fluid and sodium due to enhanced diuresis may occur which may uncommonly provoke symptoms such as dry mouth, thirst, weakness, dizziness, muscle pain and muscle cramps (e.g. calf cramps), headache, nervousness, palpitations, hypotension and orthostatic hypotension.
Excessive diuresis may leadto dehydration and hypovolaemia resulting in haemoconcentration and in rare cases resulting in convulsions, lethargy, confusion, collapse and acute renal failure. In elderly patients or in patients with venous diseases haemoconcentration may provoke thrombosis or embolism.

Hypokalaemia may result in fatigue, sleepiness, muscle weakness, paraesthesia, paresis, apathy, adynamia of smooth muscles with obstipation and meteorism or arrhythmias. Severe potassium loss may result in subileus or paralytic ileus or unconsciousness and coma.

ECG disturbances and aggravated hypersensitivity of cardiac glycosides may occur. Commonly hypermagnesuria develops, which only uncommonly results in hypomagnesuria, because magnesium is mobilised from the bones.

Development of metabolic alkalosis or aggravation of metabolic alkalosis may result from electrolyte and fluid loss.

The following adverse events also may occur independent of disturbances in the electrolyte- and fluid imbalance:

Blood and lymphatic system disorders:
Common: Thrombocytopenia (sometimes with purpura)
Uncommon: Leukopenia
Very rare: Agranulocytosis, bone marrow depression, aplastic anaemia, haemolytic anaemia, immune haemolytic anaemia due to formation of antibodies against hydrochlorothiazide during simultaneous application of methyldopa

Immune system disorders:
Rare: Hypersensitivity reactions.

Metabolism and nutrition disorders:
Very common: disturbances in the electrolyte- and fluid imbalance, especially hypokalaemia, hyponatraemia, hypochloraemia and hypercalcaemia; hyperglycaemia and glucosuria in patients without metabolic problems and those with latent or manifest diabetes mellitus or in patients with hypokalaemia; hyperuricaemia, resulting in acute gout in pre-disposed patients; elevations of serum lipids (cholesterol, triglycerides).
Very rare: Hypochloraemic alkalosis
Not known: aggravation of diabetes in patients with manifest diabetes mellitus, manifestation of a latent diabetes mellitus

Psychiatric disorders:
Rare: sleep disorders, depression

Nervous system disorders
Rare: Paraesthesia, headache, dizziness or dullness.

Eye disorders
Uncommon: Visual disorders (e.g. blurred vision, xanthopsia) impaired secretion of tears, aggravation of myopia

Cardiac disorders
Common: palpitations
Uncommon Orthostatic hypotension, especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics (which can be aggravated by alcohol, anaesthetics or sedatives).
*Rare: A*rrhythmias.

Vascular disorders:
Uncommon: Vasculitis (in single cases necrotizing vasculitis)

Respiratory, thoracic and mediastinal disorders
Uncommon: respiratory distress, acute interstitial pneumonia
Very rare: pulmonary oedema with shock, probably due to an allergic reaction

Gastrointestinal disorders
Common: Loss of appetite, gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps and abdominal pain)
Rare: constipation

Hepato-biliary disorders
Uncommon: Pancreatitis, hyperamylasemia, icterus (intrahepatic cholestasis)
Not known: in patients with pre-existing cholelithiasis, anacute cholestasis may develop, jaundice.

Skin and subcutaneous tissue disorders
Uncommon: allergic skin reactions (e.g. pruritus, erythema, photoallergic exanthema, purpura, urticaria)
Very rare: Angiitis necroticans (vasculitis) and toxic epidermal necrolysis, cutaneous lupus erythematodes, lupus erythematodes--like reactions, reactivation of cutaneous lupus erythematodes.

Renal und urinary disorders:
Very common: glucosuria
Common: reversible elevation of serum creatinine and urea
Uncommon: interstitial nephritis

Reproductive system and breast disorders
Uncommon: Impotence.

General disorders and administration site conditions:
Uncommon: drug fever

Neoplasms benign, malignant and unspecified (incl cysts and polyps):
not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

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

4.9 Overdose

Symptoms of intoxication:
Symptoms which can occur after ingestion are acute fluid loss, gastrointestinal symptoms, polyuria or oliguria, dizziness and impaired consciousness. As a result of severe hypokalemia: muscle weakness, fatigue, concentration disorders, dullness, cardiac arrhythmias, hypotension and coma. As a result of acute hyponatraemia: agitation, headache, pain or cramps, and convulsions.

Treatment of intoxication:
Treatment consists of the inducement of vomiting, the repeated administration of activated charcoal and the drinking of large amounts. Gastric lavage, where necessary (only useful shortly after intake). Maintenance of the fluid and electrolyte balance. Potassium suppletion, where necessary.
Further symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: benzothiadiazine (thiazide) diuretic.
ATC Code: C03 AA03

Thiazide diuretics particularly exert their effect in the distal part of the renal tubule by inhibiting NaCl resorption (by antagonism of the Na^+Cl carrier). The increased amount of Na^+ and water in the ductus colligens (collecting duct) and/or the increased filtration rate results in an increase in the secretion and excretion of K^+ and H^+.
In people with normal renal function, diuresis is already promoted after administration of 12.5 mg of hydrochlorothiazide. The resulting increase in the urinary excretion of sodium and chloride and the relatively small increase in potassium in the urine are dose related. The diuretic and natriuretic effect

is noticeable after 1-2 hours following the oral administration of hydrochlorothiazide, reaches its maximum after 4-6 hours and can last for 10-12 hours.

Thiazide-induced diuresis initially results in a decrease in plasma volume, the cardiac minute volume and systemic blood pressure. The renin-angiotensin-aldosterone system can be activated. The hypotensive effect continues to be maintained with the continuation of the medication, probably as a result of the decrease in peripheral resistance; the cardiac minute volume returns to the original value and the plasma volume remains somewhat lower.

With long-term administration, the antihypertensive effect of hydrochlorothiazide is dose related between 12.5 and 50 mg a day. The maximum hypotensive effect is usually reached at 50 mg a day in most patients. Increasing the dose to above 50 mg/day increases the metabolic complications and is rarely necessary from a therapeutic point of view.

If given as a monotherapy, hydrochlorothiazide appears to produce a good effect in around 40-50% of patients, just like other diuretics. In general, elderly people and black people appear to respond well to diuretics as the primary therapy.

Combined treatment with other antihypertensive agents increases the blood pressure lowering effect. In a large proportion of patients who show an unsatisfactory response to a monotherapy, a further decrease in blood pressure can be achieved in this way.

As thiazide diuretics such as hydrochlorothiazide reduce Ca^{+} excretion, these are used in order to prevent the recurrence of renal calcium oxalate stones in patients with idiopathic normocalcaemic hypercalciuria.

With long-term treatment, users of thiazide diuretics appear to have a significantly higher mineral content in their bones than non-users.

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

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Absorption
The absorption of hydrochlorothiazide administered as hydrochlorothiazide tablets amounts in total to around 70% of the dose. However, variations in absorption as a result of fasting or the intake of food

are of little clinical significance. The absorption of hydrochlorothiazide is reduced in patients who suffer from cardiac decompensation.

In the therapeutic domain, the bioavailability and maximum concentration are directly proportional to the dose. After continuous administration, the pharmacokinetics of hydrochlorothiazide do not change and the average concentration is around 100 ng/ml at a dose of 75 mg a day every day for six weeks.

Distribution
Hydrochlorothiazide accumulates in erythrocytes and reaches a maximum concentration around 4 hours after oral administration. After 10 hours, the concentration in the erythrocytes is around three times higher than in the plasma. Binding to plasma proteins of around 40-70% has been reported and the apparent volume of distribution can be estimated to be 5-6 l/kg.
Hydrochlorothiazide crosses the placenta and, in the umbilical cord, reaches a concentration which approaches the concentration in the plasma of the mother. The medicinal product accumulates in the amniotic fluid, where the concentration can be nineteen times the concentration in the umbilical cord.
Hydrochlorothiazide is excreted in the maternal milk.

Elimination
Hydrochlorothiazide is eliminated from plasma with an elimination half-life of on average 9.5 to 13 hours in the terminal elimination phase. Within 72 hours, 60-80% of an oral dose is excreted in the urine, 95% in an unchanged form and around 4% in the form of the hydrolysate 2-amino-4-chloro-m-benzene disulphonamide (ACBS). Up to 24% of an oral dose is excreted in the faeces and a negligible amount is excreted via bile.

In elderly patients, the “steady-state” concentration of hydrochlorothiazide is elevated and systemic clearance is significantly decreased compared with younger patients. For this reason, it is necessary that the treatment of elderly patients take place under strict supervision.

In patients with renal impairment (creatinine clearance between 30 and around 70 ml/min), the rate of urinary excretion is reduced and a higher maximum plasma concentration and AUC are observed. The average elimination half-life is twice as long. In these patients, a 50% dose reduction is recommended.

Hepatic diseases do not have a significant influence on the pharmacokinetics of hydrochlorothiazide and no adjustment of the dose is usually necessary.

5.3 Preclinical safety data

Acute toxicity
Animal testing of acute toxicity did not reveal a special sensitivity to hydrochlorothiazide.

Chronic toxicity/subchronic toxicity
Animal subchronic and chronic toxicity studies in dogs and rats revealed no marked results except changes in electrolyte balance.

Carcinogenesis, mutagenesis
In vitro and in vivo mutagenicity assays for gene and chromosomal mutations showed negative results.

Long-term studies with hydrochlorothiazide in rats and mice showed no relevant elevations of tumor amount in the dosage groups.

Impairment of fertility
In animal studies, hydrochlorothiazide crosses the placenta. Animal studies in rats, mice and rabbits showed no teratogenic effects.

Hydrochlorothiazide is distributed into the breast milk. Thiazide diuretics are known to inhibit lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Colloidal anhydrous silica
Maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister packaging:
5 years

Tablet container:
2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear and colourless PVC /Al blisters containing tablets. The blisters are packed in cartons.
Blister packs of 2x10 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

Hydrochlorothiazide 25 mg tablets		
Module 1.3	Product Information	Version: 2019-09-30
Module 1.3.1	Summary of Product Characteristics	

Emzor Pharmaceutical Industries Limited
Flowergate Mixed Development
Scheme.Km 1 Sagamu/Benin Expressway,
Sagamu,Ogun State.