SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

HCT-SSP 25 (Hydrochlorothiazide Tablets BP 25 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains 25 mg hydrochlorothiazide. For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

White, round biconvex tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hydrochlorothiazide is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

Hydrochlorothiazide has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

Hydrochlorothiazide is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

4.2. Posology and method of administration

Posology

Therapy should be individualized according to patient response. Use the smallest dosage necessary to achieve the required response.

Adults:

For Edema

The usual adult dosage is 25 to 100 mg daily as a single or divided dose. Many patients with edema respond to intermittent therapy, i.e., administration on alternate days or on three to five days each week. With an intermittent schedule, excessive response and the resulting undesirable electrolyte imbalance are less likely to occur.

For Control of Hypertension

The usual initial dose in adults is 25 mg daily given as a single dose. The dose may be increased to 50 mg daily, given as a single or two divided doses.

Doses above 50 mg are often associated with marked reductions in serum potassium (see also PRECAUTIONS).

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily when used concomitantly with other antihypertensive agents.

Infants and Children:

For Diuresis and For Control of Hypertension

The usual paediatric dosage is 0.5 to 1 mg per pound (1 to 2 mg/kg) per day in single or two divided doses, not to exceed 37.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per day in two divided doses may be required

Method of administration

The tablet(s) should be taken with a sufficient quantity of liquid. Duration of treatment: The duration of treatment is unlimited and depends on the type and severity of the disease. After long-term treatment, therapy with hydrochlorothiazide should be discontinued gradually.

4.3. Contraindications

Hydrochlorothiazide Tablets BP 25 mg must not be used in the following cases:

- Hypersensitivity to hydrochlorothiazide, to other thiazides or sulfonamides or to any of the excipients (see sections 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

Special warnings

Hydrochlorothiazide is generally not recommended in patients with bilateral renal artery stenosis or a single functioning kidney or with hypokalaemia. Hydrochlorothiazide is a sulfonamide. The possibility of cross-reactivity especially with other antibacterials including sulfonamides is theoretical and not clinically confirmed. Hepatic impairment Thiazides, like other diuretics may induce electrolyte imbalance, hepatic encephalopathy or hepatorenal syndrome when used to treat cirrhotic ascites. Hydrochlorothiazide should be used with caution particularly in patients with severe liver damage. Photosensitivity reactions have been reported with the use of thiazide diuretics. If a photosensitivity reaction occurs treatment should be discontinued. If re-administration of treatment is essential, areas exposed to the sun or artificial UVA should be protected.

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. Precautions for use Electrolyte imbalance Serum sodium Serum sodium levels should be monitored before treatment and at regular intervals thereafter. Thiazide diuretics may lead to hyponatraemia or an exacerbation of pre-existing hyponatraemia. In subjects with a significant decrease in serum sodium and/or a significant volume depletion, as observed in patients receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of hydrochlorothiazide treatment. A decrease in plasma sodium may initially be asymptomatic, regular monitoring is essential and needs to be more frequent in populations at risk such as the elderly, and even more in malnourished and cirrhotic patients. Monitoring is especially important in patients with ascites as a result of liver cirrhosis and in patients with oedema as a result of nephrotic syndrome. Isolated cases of hyponatremia have been observed accompanied by neurological symptoms (nausea, increasing disorientation, apathy). Thiazides should be only used after normalization of any existing sodium and/or volume depletion. Otherwise, treatment should be initiated under strict medical supervision. Serum potassium Thiazide diuretics can also lead to hypokalaemia or an exacerbation of a pre-existing hypokalaemia. Thiazides should be used with caution in patients with a disease that can cause a significant loss of potassium, such as kidney disease with loss of salts or kidney function disorders of prerenal origin (cardiogenic). The risk of hypokalaemia onset (With long term treatment, serum potassium concentration should be determined at start of treatment. A control at 3-4 weeks may be considered depending on risk factors. Then regular checks should be recommended especially in patients at risk. Uric acid As with other diuretics, hydrochlorothiazide can increase serum uric acid concentration, due to the reduction in its excretion in urine, and consequently promote hyperuricemia or the aggravation of an existing hyperuricemia. This can trigger attacks of gout in susceptible patients. The dose should be adjusted according to serum levels of uric acid. Metabolic effects Serum calcium Thiazide diuretics reduce the urinary excretion of calcium and can cause a slight, transient increase in serum calcium levels in the absence of known calcium metabolism disorders. Hydrochlorothiazide should be used with caution in patients with hypercalcemia and should be administered only after correction of any pre existing hypercalcemia. Hydrochlorothiazide should be discontinued if hypercalcemia occurs during treatment. Serum calcium levels should be

monitored regularly during treatment with thiazide diuretics. Marked hypercalcemia may be a sign of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out parathyroid function tests. Serum glucose and lipid levels Thiazide diuretics, including hydrochlorothiazide, can decrease glucose tolerance and raise serum levels of cholesterol and triglycerides. In diabetic patient dosage adjustments of insulin or oral hypoglycaemic agents may be required. Renal function and diuretics Thiazide diuretics are only fully effective when renal function is normal or only slightly impaired (evaluated, for example by calculating the creatinine clearance from serum creatinine). In the elderly, the creatinine clearance value should be adjusted by patient age, weight and sex, according to the Cockroft formula, for example:

CrCl = (140 - age) x weight / 0.814 x serum creatinine

with: the age in years, weight in kg & creatinine in micromol/l.

This formula is valid for the elderly male and should be corrected for women by multiplying the result by 0.85. Hypovolemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment, leads to a reduction in glomerular filtration. This can result in an increase in blood urea and creatinine. This transitory renal function impairment may worsen pre-existing renal impairment. Choroidal effusion, acute myopia and secondary angle-closure glaucoma Hydrochlorothiazide, a sulphonamide, 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 hydrochlorothiazide 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 sulphonamide or penicillin allergy.

Other Antihypertensive combinations It is advised to reduce the dose when combined with other anti-hypertensives, at least initially. The antihypertensive effect of ACE inhibitors, angiotensin II antagonists or renin inhibitors is potentiated by treatment that increases plasma renin activity (diuretics). Caution is advised when an ACE inhibitor, an angiotensin II antagonist or a direct renin inhibitor is administered concomitantly with hydrochlorothiazide, particularly in patients with severe sodium and/or volume depletion. Anti-doping test Hydrochlorothiazide could produce a positive analytical result in an anti-doping test. Other Lupus erythematosus: exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics, including hydrochlorothiazide. Hypersensitivity reactions to hydrochlorothiazide are more likely to occur in patients with allergies and asthma. The medicinal product contains lactose. 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

When administered concomitantly, the following drugs may cause an interaction with hydrochlorothiazide:

Medicines that affect serum potassium levels

Hypokalaemia is a predisposing factor for heart rhythm disorders (torsades de pointes, in particular) and for increasing the toxicity of certain drugs, such as digoxin. Therefore, medicines that can cause hypokalaemia are involved in many interactions. These are potassium lowering diuretics, alone or combined; stimulant laxatives; glucocorticoids; the tetracosactide and amphotericin B (IV route).

Medicines that affect serum sodium levels

Certain drugs are frequently involved in causing hyponatremia. These are diuretics, desmopressin, serotonin reuptake inhibiting antidepressants, carbamazepine and oxcarbazepine. The combination of these drugs increases the risk of hyponatremia.

Concomitant use not recommended:

Lithium:

Increased serum lithium levels with signs of lithium overdose, as in a salt-free diet (decreased urinary excretion of lithium). If this combination proves essential, serum lithium levels should be closely monitored and the lithium dose should be adjusted.

Concomitant use requiring caution:

Acetylsalicylic acid

For anti-inflammatory doses of acetylsalicylic acid (≥ 1 g per dose and / or ≥ 3 g daily) or for analgesic or antipyretic doses (≥ 500 mg per dose and / or<3 g per day).

Acute renal failure in dehydrated patients with decreased glomerular filtration secondary to decreased renal prostaglandin synthesis. In addition, reduction of the antihypertensive effect. Hydrate the patient and monitor renal function at start of treatment.

Non-steroidal anti-inflammatory drugs

Acute renal failure in at risk patients (elderly and / or dehydrated) due to reduced glomerular filtration (inhibition of vasodilatory prostaglandins due to non-steroidal anti-inflammatory drugs). In addition, reduction of the antihypertensive effect. Hydrate the patient and monitor renal function at start of treatment.

Carbamazepine

Risk of symptomatic hyponatraemia. Clinical and biological monitoring. If possible, use another class of diuretic.

Chelating resins

Chelating resins can decrease intestinal absorption and the effectiveness of other medicines taken simultaneously. In general, the resin should be taken at a time distant from that of the other medicines, with an interval of more than 2 hours, if possible.

Digitalis

Hypokalaemia increases the toxic effects of digitalis. Correct any hypokalaemia beforehand and perform clinical, electrolyte and electrocardiographic monitoring. Potassium-sparing diuretics (alone or in combination)

This reasonable combination, useful for some patients, does not rule out the occurrence of hypokalaemia or, particularly in renal failure and diabetes, of hyperkalaemia. Monitor serum potassium, possibly ECG and, if necessary, reconsider the treatment.

Angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonist

Risk of sudden hypotension and/or acute renal failure when starting or increasing the dose of an ACE inhibitor or an angiotensin II antagonist when there is pre-existing sodium depletion. In arterial hypertension, when prior diuretic treatment lead to salt depletion, you must:

- ✓ either stop the diuretic before starting treatment with the angiotensin II antagonist or AEC, and reintroduce a potassium lowering diuretic later if necessary; or give lower initial doses of the angiotensin II antagonist or ACE and gradually increase the dosage.

In patients with congestive heart failure being treated with diuretics, start with a very low dose of ACE inhibitor or angiotensin II antagonist, possibly after lowering the dose of the concomitant potassium lowering diuretic. In all cases, renal function (serum creatinine) should be monitored during the first weeks of treatment with ACE inhibitors or angiotensin II antagonists.

Medicines that may cause torsades de pointes (amiodarone, amisulpride, arsenic, artenimol, chloroquine, chlorpromazine, citalopram, cyamemazine, diphemanil, disopyramide, dofetilide, dolasetron, domperidone, dronedarone, droperidol, erythromycin, escitalopram, flupentixol, fluphenazine, halofantrine, haloperidol, hydroquinidine, hydroxyzine, ibutilide, levofloxacin, levomepromazine, lumefantrine, mequitazine, methadone, mizolastine, moxifloxacin, pentamidine, pimozide, pipamperone, piperaquine, pipotiazine, prucalopride, quinidine, sotalol, spiramycin, sulpiride, sultopride, tiapride, toremifene, vandetanib, vincamine, zuclopenthixol) Increased risk of ventricular arrhythmias, especially torsades de pointes Correct any hypokalaemia before administering the medicine and perform clinical, electrolyte and electrocardiographic monitoring.

Other potassium-lowering medicines

Increased risk of hypokalaemia. Monitoring of serum potassium with correction if required.

Iodine Contrast Media

In cases of dehydration caused by diuretics there is a greaterrisk of acute renal function impairment, especially with high doses of iodinated contrast media. Rehydration before administration of the iodinated product.

Combinations to be taken into account

Alpha-blockers for urological problems (alfuzosin, doxazosin, prazosin, silodosin, tamsulosin, terazosin) Hypotensive effect increased. Greater risk of orthostatic hypotension.

Alpha-blocker antihypertensives

Hypotensive effect. Greater risk of orthostatic hypotension.

Medicines causing orthostatic hypotension

Besides antihypertensives, many other drugs can cause orthostatic hypotension; especially nitrates, phosphodiesterase type 5 inhibitors, alpha blockers for urological problems, of tricyclic antidepressants and phenothiazines, dopamine agonists, levodopa, baclofen, amifostine. Increased risk of hypotension, especially orthostatic hypotension.

Calcium

Risk of hypercalcaemia due to reduced urinary calcium excretion.

Cyclosporin

Risk of increased creatinine without changes in ciclosporin blood levels, even in the absence of sodium depletion. Also risk of hyperuricaemia and gout-type complications. Nitrate derivatives Increased risk of hypotension, especially orthostatic hypotension.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are insufficient data on the use of hydrochlorothiazide during pregnancy, especially during the first trimester of pregnancy. Studies in animals are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimesters of pregnancy may impair foetal-placental perfusion and cause foetal and neonatal jaundice, electrolyte imbalance and thrombocytopenia. Hydrochlorothiazide must not be used in women with pregnancy oedema, hypertension or preeclampsia because there is also a risk of reduced plasma volume and placental hypo perfusion, while the progress of the clinical picture is not affected by this medicine. Hydrochlorothiazide should not be used for the treatment of essential hypertension in pregnant women except in rare cases where no other treatment could be used.

Breast-feeding

Hydrochlorothiazide is excreted in breast milk in small amounts. The use of thiazides in high doses intensifies diuresis and my inhibit milk production. The use of hydrochlorothiazide during breast-feeding is not recommended. If hydrochlorothiazide is indicated, the doses should be as low as possible.

Fertility

There are no human fertility data for hydrochlorothiazide. In animal studies, hydrochlorothiazide had no effect on fertility and conception.

4.7. Effects on ability to drive and use machines

Hydrochlorothiazide Tainex has minor or moderate influence on the ability to drive and use machines. This has to be considered especially at the beginning of therapy or when dosage is increased, when the medication is changed or when taken in combination with alcohol.

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 to <1/10

Uncommon: ≥1/1,000 to <1/100

Rare: ≥1/10,000 to <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 lead to 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:

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

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

Not known: Acute myopia, acute angle-closure glaucoma, choroidal effusion.

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, an acute 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.

Description of selected adverse

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).

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

Microcrystalline Cellulose PH 102- BP

Pregelatinized starch- BP

Sodium laurilsulfate-BP

Silicon dioxide-BP

Magnesium stearate-BP

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store below 30°C, protect from moisture.

6.5. Nature and contents of container

Clear and colourless PVC /Aluminium blisters containing tablets. 10 tablets per blister and 5 blisters in box (10x5).

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

07249/07345/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/04/2022

10. DATE OF REVISION OF THE TEXT

07/08/2023