PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

HEXAZIDE 25 (tablets)

COMPOSITION:

Each Hexazide 25 tablet contains hydrochlorothiazide 25 mg.

Inactive ingredients:

Cellulose microcrystalline, lactose monohydrate, magnesium stearate, maize starch, silica colloidal anhydrous, sodium starch glycollate (type A).

Contains sugar (lactose monohydrate 80 mg).

PHARMACOLOGICAL CLASSIFICATION:

A 18.1 Diuretics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Hydrochlorothiazide acts both as a diuretic and anti-hypertensive.

The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides have an effect on the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6 to 12 hours.

Pharmacokinetic properties:

Absorption:

Peak concentrations of hydrochlorothiazide are reached in approximately 1 to 3 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60 %.

Distribution:

Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0,83 to 1,14 ℓ/kg.

Elimination:

Hydrochlorothiazide is excreted almost entirely as unchanged substance in urine. About 60 % of the oral dose is eliminated within 48 hours. Renal clearance is about 250 to 300 mℓ/min. The terminal elimination half-life of hydrochlorothiazide is 10 to 15 hours.

Renal impairment:

In patients with impaired renal function, the rate of hydrochlorothiazide elimination is reduced. In a typical study in patients with a mean creatinine clearance of 90 mℓ/min the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients, the elimination half-life is about 34 hours.

INDICATIONS:

Oedema:

Associated with congestive cardiac failure, hepatic cirrhosis, nephrotic syndrome.

Hypertension:

Hydrochlorothiazide may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS:

Severe renal and hepatic dysfunction.

Hypersensitivity to any component of this medicine formulation or other sulphonamide-derived medicines.

Safety of use during pregnancy and lactation has not yet been established.

Patients with Addison's disease.

Refractory hypokalaemia, hypercalcaemia.

WARNINGS AND SPECIAL PRECAUTIONS:

Electrolyte imbalance:

The patient should be carefully observed for signs and symptoms of electrolyte and fluid imbalance, which include thirst, dryness of mouth, weakness, lethargy, asthenia, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, oliguria, hypotension, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

It is particularly important to make urine and serum electrolyte determinations when the patient is vomiting excessively or receiving parenteral fluids. Careful check should be kept for signs of hyponatremia, hypochloraemic alkalosis, hypokalaemia and hypomagnesemia.

Hypokalaemia may develop with hydrochlorothiazide, especially following brisk diuresis and prolonged therapy, or hepatic cirrhosis and with concomitant ACTH or steroid administration.

Hypokalaemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis.

Diuretic induced hyponatraemia may occur.

Since the urinary excretion of calcium is decreased, elevation of serum calcium, in the absence of disorders of calcium metabolism may occur. Hydrochlorothiazide therapy should be withdrawn before carrying out parathyroid function tests. Elderly patients are particularly susceptible to electrolyte imbalance.

Impaired renal function and/or azotaemia:

Hydrochlorothiazide treatment is ineffective once creatinine clearance falls below 30 mℓ/min.

Azotaemia may be precipitated or aggravated by hydrochlorothiazide.

If renal function is impaired, cumulative effects of the drug may be observed.

If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

Hepatic disease:

Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations in fluid or electrolyte balance may precipitate hepatic coma.

Metabolic and endocrine effects:

Thiazide therapy may impair glucose tolerance, whereas hypoglycaemia may occur in diabetic patients under insulin or antidiabetic therapy. Therefore, in these patients blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated. Latent diabetes mellitus may become manifest during thiazide therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy.

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Hypercalcaemia:

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 tests for parathyroid function.

Hypomagnesaemia:

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia

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

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular

pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Lactose intolerance:

HEXAZIDE 25 contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take HEXAZIDE 25.

HEXAZIDE 25 contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

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 exposure has been observed in two epidemiological studies based on Danish National cancer registry. The risk for NMSC appears to increase with long-term use. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC. Patients taking hydrochlorothiazide 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 adequate protection when exposed to sunlight 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 examination of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have previously experienced NMSC.

Other:

Exacerbation or activation of systemic lupus erythematosus and an increase in blood cholesterol have been reported. Attacks of gout may be precipitated in susceptible patients.

INTERACTIONS:

The following medicines may interact with hydrochlorothiazide when administered concurrently.

Digitalis glycosides:

Hydrochlorothiazide may enhance the toxicity of these agents by depleting serum potassium concentrations.

Cholestyramine and colestipol resins:

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Non-steroidal anti-inflammatory medicinal products:

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics.

Antidiabetic agents (insulin and oral antidiabetics):

Dosage adjustment of the antidiabetic medicinal products may be necessary.

Metformin should be used with precaution: risk of lactic acidosis induced by a possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive agents:

Additive effects. Diuretic therapy should be discontinued for 2 to 3 days prior to initiation of therapy with an ACE-inhibitor, to reduce the likelihood of first dose hypotension.

Corticosteriods and ACTH:

Severe electrolyte depletion, especially hypokalaemia.

Pressor amines:

Decreased response to pressor amines (e.g. adrenalin).

Non-depolarising skeletal muscle relaxants (e.g. tubocurarine):

The effect of non-depolarising skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Medicinal products used in the treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol):

Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazides may increase the incidence of hypersensitivity reactions of allopurinol.

Calcium salts:

Hydrochlorothiazide may increase serum calcium levels due to the decreased excretion. If calcium supplements or calcium sparing medicinal products (e.g. vitamin D therapy) must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Beta-blockers and diazoxide:

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Anticholinergic agents (e.g. atropine, biperiden):

May increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Amantadine:

Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate):

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: baclofen, amifostine.

Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics or antidepressants.

Lithium:

Hydrochlorothiazide reduces the renal clearance of lithium, thus lithium toxicity may occur. Dosage adjustments of lithium may be necessary.

Medicine/laboratory test interactions:

Hydrochlorothiazide interferes with the tests for parathyroid function (see “WARNINGS AND SPECIAL PRECAUTIONS”).

PREGNANCY AND LACTATION:

Safety of use during pregnancy and lactation has not been established (see “CONTRAINDICATIONS”).

DOSAGE AND DIRECTIONS FOR USE:

Therapy should be initiated at the lowest dose required to achieve the desired effect.

Treatment should be individualised.

Adults:

Oedema:

Usual dose is 25 to 50 mg per day. When adequate control of oedema has been achieved the patient may be maintained on one tablet per day. In order to minimise excessive response and undesirable electrolyte imbalance, the dose may be administered on alternate days or on 3 to 5 days each week.

The maximum recommended daily dose is 100 mg.

Hypertension:

Usual dose is 12,5 to 25 mg daily as a single dose. The initial dosage should be 12,5 mg, whether hydrochlorothiazide is used as a single preparation or in combination. Dosage should be adjusted until the desired blood pressure is obtained and maintained. The maximum recommended daily dose is 100 mg.

It may be necessary to decrease the dose of concomitantly administered antihypertensives in order to avoid an excessive decrease in blood pressure.

SIDE EFFECTS:

Gastrointestinal disorders:

Less frequent: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, pancreatitis.

Infections and infestations:

Frequency unknown: Sialadenitis.

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

Frequency unknown: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

Blood and lymphatic system disorders:

Less frequent: Thrombocytopaenia (sometimes with purpura).

Frequency unknown: Aplastic anaemia, haemolytic anaemia, bone marrow failure, leukopaenia, neutropaenia, agranulocytosis.

Endocrine disorders:

Frequency unknown: Diabetes mellitus inadequate control.

Cardiovascular:

Orthostatic hypotension (aggravated by barbiturates, alcohol or narcotics).

Hypersensitivity:

Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions.

Metabolism and nutrition disorders:

Frequent: Hypomagnesaemia.

Less frequent: Hypochloraemic alkalosis, hypokalaemia, hyponatraemia, glycosuria, hyperuricaemia, hypercalcaemia.

Frequency unknown: Hyperglycaemia, appetite decreased, electrolyte imbalance, hypercholesterolaemia, hypovolaemia.

Psychiatric disorders:

Frequency unknown: Restlessness.

Nervous system disorders:

Less frequent: Headache.

Frequency unknown: Light-headedness.

Eye disorders:

Frequency unknown: Xanthopsia, choroidal effusion, acute myopia, acute angle-closure glaucoma.

Vascular disorders:

Frequency unknown: Vasculitis necrotizing.

Hepatobiliary disorders:

Frequency unknown: Jaundice hepatocellular, jaundice cholestatic.

Skin and subcutaneous tissue disorders

Frequency unknown: Lupus-like syndrome, photosensitivity reactions, skin vasculitis, toxic epidermal necrolysis, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Weakness.

Renal and urinary disorders:

Frequency unknown: Renal dysfunction, interstitial nephritis, renal failure, glycosuria.

General disorders and administration site conditions:

Frequency unknown: Pyrexia.

Investigations:

Frequency unknown: Triglycerides increased.

Should side effects be moderate to severe, it is suggested that the dose of hydrochlorothiazide be reduced or that treatment be withdrawn.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT:

(See “WARNINGS AND SPECIAL PRECAUTIONS”.)

Symptoms:

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and/or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment:

Treatment is symptomatic and supportive.

IDENTIFICATION:

White to off white round, biplanar tablet with a facette and a cross score notch.

Diameter: 8,0 ± 0,2 mm.

Height: 2,6 ± 0,2 mm.

PRESENTATION:

White opaque polypropylene (PP)/aluminium blisters or polyvinylchloride (PVC)/aluminium blisters.

Each blister strip contains 10 tablets and each pack contains 30 or 100 tablets or each blister strip contains 14 tablets and each pack contains 28 tablets.

STORAGE INSTRUCTIONS:

Store in tight, well-closed containers at or below 25 °C.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

32/18.1/0419

NAME AND BUSINESS ADRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

DATE OF PUBLICATION:

Date of registration: 10 October 2000

Date of the most recent approval of the professional information: 10 August 2020

Additional country(ies) registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Namibia	Hexazide 25	NS2	04/18.1/1339
Zambia	Hexazide 25	POM	039/067

ATC Code: C03AA03 – Thiazides, plain

Name and address of manufacturer:
Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
39179 Barleben
Germany

or

Hexal AG
Industriestrasse 25
83607 Holzkirchen
Germany

[1]Company Reg. No.: 1990/001979/07