Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCTS

Disothiazide 25

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg hydrochlorothiazide.

Excipient with known effect:
Each tablet contains approximately 135 Lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Light orange, convex tablets, scored on one side.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Disothiazide is a diuretic to treat hypertension, edema.

4.2 Posology and method of administration

Posology:

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

Adults

Hypertension: The usual starting dosage is 25 or 50 mg a day as a single or divided dose. In some patients, when Disothiazide 25 is given as a single entity or in combination with other antihypertensive agents, a starting dose of 12.5 mg daily may be sufficient. Dosage should be adjusted according to blood pressure response. The maximum recommended daily dose is 50 mg.

When thiazides are used with other antihypertensives, the dose of the latter may need to be reduced to avoid excessive decrease in blood pressure.

Oedema: The usual dosage is 25 mg to 100 mg once or twice a day. Many patients respond to intermittent therapy (administration on alternate days or on three to five days each week) which may avoid an excessive response and undesirable electrolyte imbalance. The maximum recommended daily dosage is 200 mg.

The recommended dosage in premenstrual tension with oedema is 25 mg to 50 mg once or twice a day from the first morning of symptoms until onset of the menses.

Special populations

Use in renal impairment
When creatinine clearance falls below 30 mL/min thiazide diuretics are ineffective. Azotaemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with

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

Use in hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Use in the elderly
No data are available.

Children and adolescents (6 to 17 years of age):
Disothiazide 25 should be used in children 6 years of age and older due to potential swallowing difficulties and risk of choking in younger children.
For children under 6 years old, alternative treatment should be considered.

For Control of Hypertension: The usual pediatric dosage is 1 to 2 mg/kg per day in single or two divided doses, not to exceed 50 mg per day in children and adolescents 6 to 17 years of age.

4.3 Contraindications

Disothiazide must not be taken in the following cases:
- hypersensitivity to the active substance, to other thiazides, sulfonamides, or to any of the excipients listed in section 6.1
- severe renal impairment (creatinine clearance <30 ml/min and/or serum creatinine >1.8 mg/100 ml)
- anuria
- acute glomerulonephritis
- coma and hepatic precoma
- therapy-resistant hypokalaemia or hypercalcaemia
- therapy-refractory hyponatraemia
- hypovolemia
- symptomatic hyperuricaemia/gout
- hypertension during pregnancy

4.4 Special warnings and precautions for use

In cases of chronic diuretics abuse, Pseudo-Bartter syndrome resulting in oedemas may occur. The oedemas are a sign of a raised renin level, leading to secondary hyperaldosteronism.

Electrolytes
Thiazide diuretics may trigger hypokalaemia or increase pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients suffering from diseases that cause an increased loss of potassium, such as nephropathies with salt excretion and prerenal (cardiogenic) deterioration of the renal function. It is recommended to balance any hypokalaemia possibly accompanied by hypomagnesaemia before beginning treatment with thiazides. The serum potassium and serum magnesium levels should be monitored at regular intervals. All patients taking thiazide diuretics should be monitored for electrolyte imbalance, and in particular potassium.

As with all thiazide diuretics, HCT-induced potassium excretion is dose-dependent. In long-term treatment, the serum potassium concentration should be checked at the beginning of treatment and 3-4 weeks later. If the potassium balance is not influenced by other factors (such as vomiting, diarrhoea, changes in kidney function), a subsequent check-up should be carried out at regular intervals.

An additional titrated administration of oral potassium salts (e.g. KCl) can be considered for patients who are treated with digitalis (see section 4.5), who have symptoms of coronary heart disease (unless they are also receiving an ACE inhibitor), as well as for patients taking a high dose of a β-agonist, and in all cases in which serum potassium levels are below 3.0 mmol/l. If oral potassium salts are not tolerated, Disothiazide can be

combined, if necessary, with a potassium-sparing diuretic.

In cases of combination treatment with potassium salts, the maintenance or normalization of the potassium balance should in any case be monitored at close intervals. If there is hypokalaemia accompanied by symptoms (such as muscular weakness, paresis or changes in the ECG), administration of Disothiazide should be discontinued.

Concomitant treatment with Disothiazide and a potassium salt or a potassium-sparing diuretic should be avoided in patients who also take ACE inhibitors, ARBs or DRIs.

Thiazide diuretics may trigger hyponatraemia or increase pre-existing hyponatraemia. In patients with severe sodium or volume depletion, as well as in patients taking high doses of diuretics, symptomatic hypotension may appear in rare cases after hydrochlorothiazide treatment has started. In isolated cases, hyponatraemia with associated neurological symptoms (nausea, progressive disorientation and apathy) was observed. Thiazide diuretics should be used only after balancing any pre-existing sodium and/or volume depletion. Otherwise, the treatment should be initiated only under close medical supervision. Regular monitoring of serum sodium concentration is recommended.

Especially in elderly patients, patients with ascites caused by liver cirrhosis and in patients with oedemas caused by nephrotic syndrome, monitoring of serum electrolytes is indicated. In patients with nephrotic syndrome, Disothiazide should be administered only under close supervision and only to patients with normal potassium levels which show no indication of a volume depletion or severe hypoalbuminaemia.
Due to decreased uric acid clearance, Disothiazide, like other diuretics, may increase the serum uric acid level and cause or worsen hyperuricaemia and trigger gout in susceptible patients.

Metabolic effects
Thiazide diuretics, including hydrochlorothiazide, can alter glucose tolerance and increase the plasma concentration of cholesterol and triglycerides.

Thiazides reduce calcium excretion through the kidneys and may cause a slight increase of serum calcium levels, even if there are no known calcium metabolism disorders. Since hydrochlorothiazide may increase plasma calcium concentration, it should be administered with caution to patients with hypercalcaemia. Marked hypercalcaemia, which does not respond to thiazide discontinuation or which is > 12 mg/dl, may be a sign for an underlying, thiazide-independent hypercalcaemic process.

Pathological changes in the parathyroid gland, accompanied by hypercalcaemia and hyperphosphataemia, were observed in a small number of patients under long-term treatment with thiazides. When hypercalcaemia occurs, further diagnostics is indicated.

During treatment with Disothiazide, patients should ensure that they consume an adequate amount of fluid, and, due to increased potassium losses, they should eat foods that are rich in potassium (e.g. bananas, vegetables, nuts).

Patients with renal impairment
See section 4.2 Posology and method of administration.

Patients with hepatic impairment
See section 4.2 Posology and method of administration.

Choroidal effusion, acute myopia and secondary closed-angle glaucoma
Sulfonamides and sulfonamide derivatives may trigger an idiosyncratic reaction which may lead to a choroidal effusion accompanied by a visual field defect, to transient myopia and to acute closed-angle glaucoma. The symptoms include onset of decreased visual acuity or eye pain and typically appear within hours to weeks after the initiation of treatment. Untreated closed-angle glaucoma may lead to a permanent loss of vision.

The primary treatment consists of discontinuation of hydrochlorothiazide administration as soon as possible. Rapid medicinal or surgical treatment may be considered if intraocular pressure remains out of control. Risk factors for the development of closed-angle glaucoma may be known sulfonamide or penicillin allergies.

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).

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Disothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Particularly careful monitoring is necessary in cases of
- hypotension
- cerebrovascular circulatory disorders
- coronary heart disease

Cerebrovascular insufficiency and coronary heart disease
Disothiazide may only be administered to these patients under close medical supervision.

Additional information
The hypotensive effect of ACE inhibitors, ARBs and DRIs is particularly enhanced by drugs which increase plasma renin activity (e.g. diuretics). When administering an ACE inhibitor (or ARBs or DRIs) in addition to Disothiazide, caution should be exercised, particularly in patients with severe sodium and/or volume depletion.

Latent lupus erythematosus might be triggered by thiazides.

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

Disothiazide may produce a positive result in doping tests.

Paediatric population
See section 4.2 Posology and method of administration.

Elderly patients (above 65 years)
See section 4.2 Posology and method of administration.

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

The hypotensive effect of Disothiazide may be enhanced by other diuretics, antihypertensive drugs, guanethidine, methyldopa, calcium antagonists, ACE inhibitors, ARBs, DRIs, β-receptor blockers, nitrates, barbiturates, phenothiazines, tricyclic antidepressants, vasodilators or alcohol consumption.

There is a risk of a massive decrease in blood pressure as well as deterioration of the renal function in the initial stage of the treatment in case additional ACE inhibitors (e.g. captopril) are administered while the patient is treated with Disothiazide. For this reason, diuretic treatment should be discontinued 2–3 days before starting treatment with an ACE inhibitor in order to minimize the possibility of hypotension at the beginning of the treatment.

Salicylates and other non-steroidal anti-inflammatory drugs (e.g. indomethacin) may reduce the antihypertensive and diuretic effect of Disothiazide. When taking high doses of salicylate, the toxic effect of the salicylates on the central nervous system may worsen. In patients who have developed hypovolaemia during Disothiazide treatment, concomitant administration of non-steroidal anti-inflammatory drugs may trigger acute renal failure.

Concomitant administration of thiazides (including hydrochlorothiazide) and allopurinol can potentially increase the frequency of hypersensitivity reactions to allopurinol.

Concomitant administration of thiazides and amantadine may increase the risk of side effects caused by amantadine.

There is an increased risk of hyperglycaemia in case of concomitant administration of Disothiazide and β-receptor blockers.

The effect of insulin or oral antidiabetic drugs, of uric acid-lowering drugs as well as noradrenaline and adrenaline may be reduced during concomitant treatment with Disothiazide. Dose adjustment of insulin or oral antidiabetic drugs may be necessary.

During concomitant treatment with cardiac glycosides, it must be considered that if hypokalaemia and/or hypomagnesaemia develop during Disothiazide treatment, the sensitivity of the myocardium to cardiac glycosides increases and the effects and side effects of cardiac glycosides are enhanced accordingly.

Concomitant administration of Disothiazide and kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, carbenoxolone, penicillin G, salicylates, amphotericin B, anti-arrhythmic drugs or laxatives may result in increased potassium losses.

Concomitant use of natriuretic diuretics and antidepressants, antipsychotic or antiepileptic drugs may result in increased losses of sodium. Caution is required for long-term use of these medicinal products.

Concomitant use of thiazide diuretics and cytotoxic agents (e.g. cyclophosphamide, fluorouracil, methotrexate) may cause decreased renal excretion of cytotoxic agents. Increased bone marrow toxicity (especially granulocytopenia) must be expected.

The bioavailability of thiazide diuretics may be increased by anticholinergics (e.g. atropine, biperiden). This is probably due to a reduction of gastrointestinal motility and of the gastric emptying rate. By contrast, prokinetic drugs such as cisapride may reduce the bioavailability of thiazide diuretics.

Diuretics increase the lithium levels in the plasma. Since concomitant use of Disothiazide and lithium leads to an increased cardio-toxic and neurotoxic effect of lithium as a result of the reduced excretion of lithium, lithium levels in patients treated with Disothiazide and lithium must be monitored. In patients in whom lithium has induced polyuria, diuretics may have a paradoxical antidiuretic effect.

The effects of curare-like muscle relaxants can be enhanced or prolonged by Disothiazide. In case Disothiazide cannot be discontinued prior to the use of peripheral curare-like muscle relaxants, the anaesthetist must be notified of the Disothiazide treatment.

Concomitant use of colestyramine or colestipol reduces the absorption of Disothiazide. Nevertheless, alternating intake of hydrochlorothiazide and the resin in such a way that hydrochlorothiazide is taken at least 4 hours before or 4-6 hours after the administration of the resin might possibly minimize interaction.

Concomitant intake of vitamin D can reduce calcium excretion in the urine and increase calcium levels in the serum.

If simultaneously taken with calcium salts, hypercalcaemia might occur due to the increase of renewed tubular calcium intake.

Concomitant intake of Cyclosporine may increase the risk of hyperuricaemia and gout-like complications.

Thiazides may intensify the hyperglycaemic action of diazoxide.

During concomitant administration of methyldopa, haemolysis caused by antibody production against hydrochlorothiazide has been described occasionally.

Adrenergic amines: Hydrochlorothiazide may reduce reaction to adrenergic amines such as noradrenaline. Nevertheless, the clinical consequences of this effect do not justify the exclusion of their use.

4.6 Fertility, pregnancy and lactation

Pregnancy
Only limited experience is available regarding the use of hydrochlorothiazide during pregnancy, especially during the first trimester. Results from animal studies are insufficient.

Hydrochlorothiazide crosses the placental barrier. Due to the pharmacological mechanism of hydrochlorothiazide, there is a risk of fetoplacental perfusion disorders and fetal and neonatal effects like icterus, electrolyte balance disorders and thrombocytopenia in the course of the second and third trimesters of pregnancy.
Due to the risk of reduced plasma volume and placental hypoperfusion, hydrochlorothiazide should not be used in cases of gestational oedemas, or a preeclampsia.

Breast-feeding
Small quantities of hydrochlorothiazide pass into the breast milk. Thiazide diuretics used in high doses for intensive diuresis may inhibit lactation. Using Disothiazide during breast-feeding is not recommended. If Disothiazide is administered during breast-feeding, the dose should be kept as low as possible.

Fertility
No data are available concerning the effect of hydrochlorothiazide on human fertility. 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

Treatment of high blood pressure with this medicinal product requires regular medical check-ups. As reactions differ individually, the ability to drive, to use machines or work without a secure grip might be impaired. This is especially true at the beginning of treatment, at dose increase and change of medication as well as in combination with alcohol.

4.8 Undesirable effects

Undesirable effects (table 1) are listed according to their frequency, with the most frequent listed first.
The following description is used:

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

Table 1

Metabolism and nutrition disorders	
Very common:	Especially in high doses, hypokalaemia and increase of serum lipids
Common:	Hyponatraemia, hypomagnesaemia and hyperuricaemia, lack of appetite
Rare:	Hypercalcaemia, hyperglycaemia, glucosuria and deterioration of the diabetic metabolic status
Very rare:	Hypochloraemic alkalosis
Skin and subcutaneous tissue disorders	
Common:	Urticaria and other forms of skin rash
Rare:	Photosensitization
Very rare:	Toxic epidermal necrolysis, cutaneous Lupus erythematosus, lupus-like reactions, reactivation of cutaneous Lupus erythematosus
Gastrointestinal disorders	
Common:	Mild nausea and vomiting
Rare:	Gastrointestinal complaints, constipation and diarrhoea
Very rare:	Pancreatitis
Hepatobiliary disorders	
Rare:	Intrahepatic cholestasis, icterus
Vascular disorders	
Common:	Orthostatic hypotension, enhanced by alcohol, anaesthetics or sedatives
Cardiac disorders	
Rare:	Arrhythmia
Nervous system disorders	
Rare:	Headache, vertigo, depression and paraesthesia
Psychiatric disorders	
Rare:	Insomnia
Eye disorders	
Rare:	Deterioration of vision, especially in the first weeks of treatment
Blood and lymphatic system disorders	
Rare:	Thrombocytopenia (sometimes with purpura)
Very rare:	Leukopenia, agranulocytosis, bone marrow depression and haemolytic anaemia
Reproductive system and breast disorders	
Common:	Erectile dysfunction
Immune system disorders	
Very rare:	Necrotizing vasculitis, hypersensitivity reactions – respiratory distress syndrome, including pneumonia and pulmonary oedema

Adverse events observed post-marketing:

The following adverse events (table 2) were identified from post-marketing experience. Since these events were reported voluntarily by a population of unknown size, it is not always possible to reliably determine their frequency.

Table 2

Respiratory, thoracic and mediastinal disorders	
Very rare:	Acute respiratory distress syndrome (ARDS) (see section 4.4)
Blood and lymphatic system disorders	
Not known:	Aplastic anaemia
Eye disorders	
Not known:	Closed-angle glaucoma, choroidal effusion
Skin and subcutaneous tissue disorders	
Not known:	Erythema multiforme
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Not known:	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Musculoskeletal and connective tissue disorders	
Not known:	Muscle cramps
Renal and urinary disorders	
Not known:	Acute renal insufficiency, kidney disorders
General disorders and administration site conditions	
Not known:	Pyrexia, asthenia

Description of selected adverse reactions

Cases of choroidal effusion accompanied by a visual field defect were reported after the use of thiazides and thiazide-like diuretics.

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 suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

Symptoms of intoxication
The clinical picture of acute or chronic overdose depends on the extent of the fluid and electrolyte loss.

In case of pronounced fluid and sodium losses, overdosage may lead to thirst, feelings of weakness and dizziness, vomiting, muscle pains and muscle cramps (e.g., cramps in the calf), headaches, tachycardia, hypotension and orthostatic regulation disorders; dehydration and hypovolaemia may result in haemoconcentration, convulsions, drowsiness, lethargy, confusion, circulatory collapse or acute renal failure. Disorders of the electrolyte balance with cardiac arrhythmias may occur.

Fatigue, muscular weakness, paraesthesia, paresis, apathy, meteorism and constipation or cardiac arrhythmias may occur due to hypokalaemia. Severe potassium losses may result in paralytic ileus or impaired consciousness up to hypokalaemic coma.

Treatment of intoxication
In the event of an overdose, treatment with Disothiazide must be discontinued immediately.

In all cases of an overdose, generally supportive measures should be applied.

Therapeutic measures
- In case of hypovolemia: Volume substitution
- In case of electrolyte imbalance: Substitution of electrolytes (e.g., potassium substitution in case of hypokalaemia)
- In case of circulatory collapse: Shock position, if necessary, shock therapy

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Thiazide diuretic;
ATC code: C03AA03

Mechanism of action
Hydrochlorothiazide is a benzothiadiazine derivative which primarily causes an increased excretion of electrolytes and secondarily increases the urinary flow due to osmotically bound water.

Hydrochlorothiazide inhibits sodium absorption predominantly in the distal tubule, with a maximum of approximately 15% of the glomerular filtrated sodium being excreted. The extent of chloride excretion corresponds almost to the amount of sodium excretion. Hydrochlorothiazide also causes the increase of potassium excretion, which is mainly determined by the potassium secretion in the distal tubule and the collecting duct (increased exchange between sodium and potassium ions). High doses of hydrochlorothiazide may result in an increased excretion of bicarbonate due to carbonic anhydrase inhibition, which alkalizes urine.
Acidosis and alkalosis do not have an essential influence on the saluretic or diuretic effect of hydrochlorothiazide.

The glomerular filtration rate is initially slightly reduced.
During long-term treatment with hydrochlorothiazide, calcium excretion through the kidneys is reduced, which may result in hypercalcaemia. In hypertensive patients, hydrochlorothiazide has a hypotensive effect; this mechanism has not yet been sufficiently clarified. It is discussed, among other things, that the effect of thiazide diuretics, which reduce the peripheral vessel tonus, is the result of a decrease of sodium concentration in the vascular wall and, consequently, of a decreased responsiveness of the vascular wall to noradrenaline.

In patients with chronic renal insufficiency (creatinine clearance <30 ml/min and/or serum creatinine > 1.8 mg/100 ml), hydrochlorothiazide is practically ineffective.

In patients with renal and ADH sensitive diabetes insipidus, hydrochlorothiazide has an antidiuretic effect.

The diuretic duration of action of hydrochlorothiazide is 10 to 12 hours, depending on the dose; the antihypertensive duration of action can last up to 24 hours.

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 and distribution
Following oral administration, 80% of hydrochlorothiazide is absorbed from the gastrointestinal tract. Systemic availability is approximately 70%. Maximum plasma levels are usually measured after 2–5 hours. The plasma protein binding of hydrochlorothiazide is 64%; the relative volume of distribution is 0.5 to 1.1 l/kg.

In healthy subjects, more than 95% of hydrochlorothiazide is excreted unchanged through the renal system.

Elimination
At normal renal function, elimination half-life is to 6–8 hours. It increases in patients with limited renal function and takes as long as approximately 20 hours in patients with terminal renal insufficiency.

The diuretic effect begins within 1–2 hours.

5.3 Preclinical safety data

Acute toxicity
The examination of the acute toxicity of hydrochlorothiazide in animal studies has not shown any special sensitivities.

Chronic toxicity / subchronic toxicity
Examinations regarding subchronic and chronic toxicity in animals (dogs, rats) yielded no conspicuous findings except changes in the electrolyte balance.

Mutagenic and carcinogenic potential
The mutagenic potential was examined in a series of *in vitro* and *in vivo* test systems. While some positive results were observed in the *in vitro* studies, all *in vivo* studies yielded negative results. It can be concluded that there is no relevant mutagenic potential *in vivo*.

Long-term studies with hydrochlorothiazide have been carried out in rats and mice and did not show any relevant increase in the number of tumors in the dosage groups.

Reproductive toxicity
Hydrochlorothiazide was not teratogenic and did not affect fertility and conception. Studies with three animal species (rat, mouse, rabbit) showed no indication of teratogenic effects with doses that were at least 10 times higher than the recommended dose of approx. 1 mg/kg in humans. Weight loss in young suckled rats was related to the high doses (15 times higher than the dose in humans) and the diuretic action of hydrochlorothiazide and the subsequent effects on milk production (see section 4.6).

In humans, there is experience in using hydrochlorothiazide during pregnancy in more than 7,500 mother-and-child pairs. Among these, 107 pregnant women were exposed in the course of the first trimester. It is suspected that using hydrochlorothiazide during the second half of pregnancy can cause thrombocytopenia in newborns. Disruptions of the electrolyte balance in pregnant women may affect the fetus.
Small quantities of hydrochlorothiazide pass into the breast milk. Thiazide diuretics are known to inhibit lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Magnesium stearate
Carmellose sodium
Silica colloidal anhydrous
Orange lake (E-110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister.

Pack sizes: 10, 25, 28, 30, 50, 500 or 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special precautions.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd., 1 Dexcel St., Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER

032-85-21827-00

Revised in February 2025 according to MOH guidelines.