DITHIAZIDE™ 25 MG TABLETS

(HYDROCHLOROTHIAZIDE)

1. NAME OF THE MEDICINE

Hydrochlorothiazide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Dithiazide tablet contains 25 mg hydrochlorothiazide as the active ingredient.

Hydrochlorothiazide is a white, or practically white, crystalline powder which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

List of excipients with known effect: Lactose monohydrate.

This medicine contains sugars as lactose.

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Dithiazide 25 mg tablets are round, light orange, flat face, bevelled edge tablets bisected on one side, debossed '2083' above the bisect and TEVA debossed on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Dithiazide is indicated for:

Hypertension: May be used alone or in combination with other antihypertensive drugs.

Oedema: Associated with congestive heart failure, hepatic cirrhosis, nephrotic syndrome, acute glomerulonephritis, chronic renal failure, premenstrual tension, and drug induced oedema. (See Section 4.4 Special Warnings and Precautions for Use)

4.2 DOSE AND METHOD OF ADMINISTRATION

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 Dithiazide 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 100 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.

Infants and Children

The usual oral paediatric dosage of Dithiazide is 2.5 mg/kg of body weight per day in two doses. Infants under six months of age may require up to 3.5 mg/kg/day in two doses.

On this basis, infants up to two years of age may be given 12.5 mg to 37.5 mg of Dithiazide daily in two doses. Children from 2 to 12 years of age may be given 37.5 mg to 100 mg daily in two doses. Doses in both age groups should be based on body weight.

4.3 CONTRAINDICATIONS

Dithiazide is contraindicated in anuria and hypersensitivity to any component of this product or to other sulphonamide-derived drugs. See also Section 4.6 Fertility, Pregnancy and Lactation, Use in Pregnancy and Use in Lactation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical 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.

Combination use of ACE-inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

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. See Section 4.8 Adverse Effects (Undesirable Effects).

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.

Electrolyte imbalance

Careful check should be kept for signs of fluid and electrolyte imbalance: namely, hyponatraemia, hypochloraemic alkalosis, hypokalaemia and hypomagnesaemia. It is particularly important to make serum and urine electrolyte determinations when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalaemia may develop with hydrochlorothiazide as with any other potent diuretic, especially with brisk diuresis, after prolonged therapy or when severe cirrhosis is present. Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).

Diuretic induced hyponatraemia is usually mild and asymptomatic. In a few patients hyponatraemia may become severe and symptomatic. Such patients require immediate attention and appropriate treatment.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Metabolic

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

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Other

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

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 available.

Paediatric use

See Section 4.2 Dose and Method of Administration.

Effects on laboratory tests

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see Section 4.4 Special Warnings and Precautions for Use).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

When given concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Anti Diabetic drugs - (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect. Diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with an ACE inhibitor to reduce the likelihood of first dose hypotension.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. adrenaline): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, non-depolarising (e.g. tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package inserts for lithium preparations before use of such preparations.

Non-steroidal Anti-inflammatory Drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Dithiazide is Pregnancy Category C- Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Thiazides, related diuretics and loop diuretics enter the fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like frusemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy products of this type should therefore only be given on sound indications, and then in the lowest effective dose.

The routine use of diuretics in otherwise healthy pregnant women with or without mild oedema is not indicated and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment oftoxaemia.

Thiazides cross the placental barrier and appear in cord blood.

Use of Dithiazide when pregnancy is present or suspected requires that the benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which occurred in the adult.

Use in lactation

Thiazides appear in breast milk. If use of the drug is deemed essential, the patient should stop breastfeeding.

4.7 EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Eye disorders: Choroidal effusion (frequency not known). Cases of choroidal effusion with visual field defect have been reported after the use of thiazide diuretics.

Gastrointestinal System: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialoadenitis.

Central Nervous System: Dizziness, vertigo, paraesthesias, headache, xanthopsia.

Haematological: Leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia.

Cardiovascular: Hypotension, including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotising angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions, toxic epidermal necrolysis.

Metabolic: Hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance including hyponatraemia and hypokalaemia.

Renal: Renal dysfunction; interstitial nephritis; renal failure.

Other: Muscle spasm, weakness, restlessness, transient blurred vision.

Postmarketing experience

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

Non-melanoma skin cancer: 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 71,553 cases of BCC and of 8,629 cases of SCC matched to 1,430,883 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).

Whenever side effects are moderate, or severe, thiazide dosage should be reduced or therapy withdrawn.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

In the event of overdosage, symptomatic and supportive measures should be employed. If ingestion is recent, emesis should be induced or gastric lavage performed. Dehydration, electrolyte imbalance, hepatic coma and hypotension should be corrected by established procedures. If required, give oxygen or artificial respiration for respiratory impairment.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dithiazide (hydrochlorothiazide) is a diuretic and antihypertensive. Dithiazide interferes with the distal renal tubular mechanism of electrolyte reabsorption. This compound increases the excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium, magnesium and bicarbonate. Urinary calcium excretion may be decreased.

Dithiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. How thiazides control hypertension is unknown. Dithiazide does not usually affect normal blood pressure.

Hydrochlorothiazide has properties qualitatively similar to chlorothiazide, although it is about 10 times as potent, on a weight basis. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

Distribution

Hydrochlorothiazide crosses the placental but not the blood-brain barrier, and is excreted in breastmilk.

Metabolism and Excretion

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. The plasma half-life of hydrochlorothiazide is 5.6 - 14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are: lactose monohydrate, calcium hydrogen phosphate dihydrate, maize starch, sunset yellow FCF and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

Dithiazide is supplied in a bottle containing 100 tablets.

Phebra product code - TAB006

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

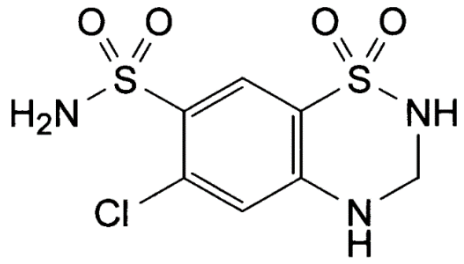
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name: 6-chloro-3,4-dihydro-2*H*-1,2, 4-benzothiadiazine-7-sulphonamide 1,1-dioxide

The molecular weight of the compound is 297.7. The molecular formula is $C_7H_8ClN_3O_4S_2$

Chemical structure



CAS number
58-93-5.

7. MEDICINE SCHEDULE (POISON STANDARD)

Schedule 4– Prescription Only Medicine

8. SPONSOR

[2]Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.

Telephone: 1800 720 020

9. DATE OF FIRST APPROVAL

24 Jan 2003

10. DATE OF REVISION

08 Dec 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2	Included information on "List of excipients with known effect"

[1] AUST R 92060
[2] Phebra and the Phi symbol are trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.