SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF FINISHED PHARMACEUTICAL PRODUCT

ASTHIAZIDE (Hydrochlorothiazide Tablets USP 25 mg)

2. Strength (composition):

Each uncoated tablet contains:

Hydrochlorothiazide USP 25 mg

3. Pharmaceutical dosage form:

Uncoated tablet

Yellow coloured, circular, slightly biconvexed uncoated tablet with a score in the middle onone side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydrochlorothiazide tablets are indicated as adjunctive therapy in edema associated withcongestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.Hydrochlorothiazide tablets have also been found useful in edema due to various forms ofrenal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renalfailure.

Hydrochlorothiazide tablets are indicated in the management of hypertension either as thesole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in themore severe forms of hypertension.

Use in Pregnancy: Routine use of diuretics during normal pregnancy is inappropriate andexposes mother and foetus to unnecessary hazard. Diuretics do not prevent development oftoxemia of pregnancy and there is no satisfactory evidence that they are useful in thetreatment of toxemia.

Edema during pregnancy may arise from pathologic causes or from the physiologic andmechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema isdue to pathologic causes, just as they are in the absence of pregnancy. Dependent edema inpregnancy, resulting from restriction of venous return by the gravid uterus, is properly treatedthrough elevation of the lower extremities and use of support stockings. Use of diuretics tolower intravascular volume in this instance is illogical and unnecessary. During normalpregnancy there is hypervolemia which is not harmful to the fetus or the mother in

theabsence of cardiovascular disease. However, it may be associated with edema, rarelygeneralized edema. If such edema causes discomfort, increased recumbency will oftenprovide relief. Rarely this edema may cause extreme discomfort which is not relieved by rest.

In these instances, a short course of diuretic therapy may provide relief and be appropriate.

4.2 Posology and method of administration

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

Adults: Edema: The usual starting dosage is 25 to 100 mg a day given in a single dose or in 2divided doses. Many patients respond to intermittent therapy (administration on alternatedays or on 3 to 5 days each week) which may avoid an excessive response and undesirableelectrolyte imbalance.

The maximum recommended daily dosage is 100 mg.

Hypertension: The usual starting dosage is 25 mg a day as a single or divided dose.In some patients, when hydrochlorothiazide is given as a single entity or in combination withother antihypertensive agents, a starting dose of 12.5 mg daily may be sufficient. Dosageshould be adjusted according to blood pressure response.

The maximum recommended daily dosage is 50 mg.

When thiazides are used with other anti-hypertensive, the dose of the latter may need to bereduced to avoid excessive decrease in blood pressure.

Infants and Children: The usual paediatric dosage is 2.5 mg/kg of body weight/day in 2doses. Infants under 6 months of age may require up to 3.5 mg/kg/day in 2 doses.On this basis, infants up to 2 years of age may be given 12.5 to 37.5 mg daily in 2 doses.

Children from 2 to 12 years of age may be given 37.5 to 100 mg daily in 2 doses. Dosage inboth age groups should be based on body weight.

Method of administration

Oral

4.3 Contraindications

Hypersensitivity to this product or to other sulfonamide-derived drugs

4.4 Special Warning & Precaution for use

Use with caution in severe renal disease. In patients with renal disease, thiazides mayprecipitate azotemia. Cumulative effects of the drug may develop in patients with impairedrenal function.

Thiazides should be used with caution in patients with impaired hepatic function orprogressive liver disease, since minor alterations of fluid and electrolyte balance mayprecipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchialasthma.The possibility of exacerbation or activation of systemic lupus erythematosus has beenreported.

Lithium generally should not be given with diuretics.

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, asulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia andacute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity orocular pain and typically occur within hours to weeks of drug initiation. Untreated acuteangle-closure glaucoma can lead to permanent vision loss. The primary treatment is todiscontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatmentsmay need to be considered if the intraocular pressure remains uncontrolled. Risk factors fordeveloping acute angle-closure glaucoma may include a history of sulfonamide or penicillinallergy.

PRECAUTIONS:

General:

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyteimbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum andurine electrolyte determinations are particularly important when the patient is vomitingexcessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyteimbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy,drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular

fatigue,hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea andvomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present orafter prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia.Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate theresponse of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Hypokalemia may be avoided or treated by use of potassium sparing diuretics or potassiumsupplements such as foods with high potassium content.Although any chloride deficit is generally mild and usually does not require specifictreatment except under extraordinary circumstances (as in liver disease or renal disease),chloride replacement may be required in the treatment of metabolic alkalosis.Dilutionalhyponatremia may occur in edematous patients in hot weather; appropriate therapyis water restriction, rather than administration of salt, except in rare instances when thehyponatremia is life threatening. In actual salt depletion, appropriate replacement is thetherapy of choice. Hyperuricemia may occur or acute gout may be precipitated in certainpatients receiving thiazides.In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may berequired. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus maybecome manifest during thiazide therapy.The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.If progressive renal impairment becomes evident, consider withholding or discontinuingdiuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium;this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent andslight elevation of serum calcium in the absence of known disorders of calcium metabolism.Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should bediscontinued before carrying out tests for parathyroid function.Increases in cholesterol and triglyceride levels may be associated with thiazide diuretictherapy.

4.5 Interaction with other medicinal products 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.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug maybe required.

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

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in thepresence of anionic exchange resins. Single doses of either cholestyramine or colestipolresins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tractby up to 85% and 43% respectively.

Corticosteroids, ACTH: intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., adrenaline): Possible decreased response to pressor amines but notsufficient to preclude their use.

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

Lithium: Diuretic agents reduce the renal clearance of lithium and add a high risk of lithiumtoxicity; concomitant use is not recommended. Refer to the Product Monographs for lithiumpreparations before use of such preparations.

NSAIDs: In some patients, the administration of NSAIDs can reduce the diuretic, natriureticand antihypertensive effects of diuretics.

4.6 Pregnancy and lactation:

Teratogenic Effects - Pregnancy Category B:

Studies in which hydrochlorothiazide was orally administered to pregnant mice and ratsduring their respective periods of major organogenesis at doses up to 3000 and 1000 mghydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.There are, however, no adequate and well-controlled studies in pregnant women. Becauseanimal reproduction studies are not always predictive of human response, this drug should beused during pregnancy only if clearly needed.Non-teratogenic Effects: Thiazides cross the placental

barrier and appear in cord blood. Thereis a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactionsthat have occurred in adults.

Nursing Mothers:

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions innursing infants, a decision should be made whether to discontinue nursing or to discontinuehydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use:

There are no well-controlled clinical trials in pediatric patients. Information on dosing in thisage group is supported by evidence from empiric use in pediatric patients and publishedliterature regarding the treatment of hypertension in such patients

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse reactions have been reported and, within each category, are listed inorder of decreasing severity.

Body as a Whole: Weakness

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

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrh oea, vomiting,sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia,thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneousvasculitis), respiratory distress including pneumonitis and pulmonary edema,photosensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis .

Skin: Erythema multiforme including Stevens-Johnson Syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced ortherapy withdrawn.

4.9 Overdose

The most common signs and symptoms observed are those caused by electrolyte depletion(hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessivediuresis. If digitalis has also been administered, hypokalemia may accentuate cardiacarrhythmias.In the event of overdosage, symptomatic and supportive measures should be employed.Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyteimbalance, hepatic coma and hypotension by established procedures. If required, give oxygenor artificial respiration for respiratory impairment. The degree to which hydrochlorothiazideis removed by hemodialysis has not been established.The oral LD 50 of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Low-ceiling Diuretics, Thiazides

ATC code: C03AA03

Mechanism of action

Hydrochlorothiazide is transported from the circulation into epithelial cells of the distalconvoluted tubule by the organic anion transporters OAT1, OAT3, and OAT4.6,3 From thesecells, hydrochlorothiazide is transported to the lumen of the tubule by multidrug resistanceassociated protein 4 (MRP4).

Normally, sodium is reabsorbed into epithelial cells of the distal convoluted tubule andpumped into the basolateral interstitium by a sodium-potassium ATPase, creating aconcentration gradient between the epithelial cell and the distal convoluted tubule thatpromotes the reabsorption of water.

Hydrochlorothiazide acts on the proximal region of the distal convoluted tubule, inhibitingreabsorption by the sodium-chloride symporter, also known as Solute Carrier Family 12Member 3 (SLC12A3). Inhibition of SLC12A3 reduces the magnitude of the concentrationgradient between the epithelial cell and distal convoluted tubule, reducing the reabsorption ofwater.

5.2 Pharmacokinetic Properties

Pharmacokinetics and Metabolism

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. Whenplasma levels have been followed for at least 24 hours, the plasma half-life has beenobserved to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose iseliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not theblood-brain barrier and is excreted in breast milk.

5.3 Preclinical safety data

No relevant pre-clinical data has been generated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Calcium Hydrogen Phosphate

Lactose

Sodium Lauryl Sulfate

Ferric oxideyellow

Maize starch

Povidone K 30

Purified Water

Colloidal Anhydrous Silica

Pregelatinized Starch

Magnesium Stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

Keep out of reach of children.

6.5 Nature and contents of container

10 x10's PVDC Blister Pack

7. Marketing authorization holder

AS PHARMACEUTICALS,

No. 1/134, B4, Kuthubi Complex,

2nd Avenue, 6thcross street,

Vettuvankeni, Chennai – 600115, India

8. Marketing authorisation number(s)

06252/07871/REN/2021

9. Date of first registration/ renewal of the registration

Date of first authorisation: 29.06.2017

Date of latest renewal: 24.07.2021

10. Date of revision of the text

07/2023