Proposed Clean Professional Information for Medicines for Human Use: Hydrochlorothiazide 25 Gulf

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Hydrochlorothiazide 25 Gulf tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Hydrochlorothiazide 25 mg

Contains sugar: Lactose anhydrous 72 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white, round shaped, biconvex, uncoated tablet with a central break line on one side and plain on the other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydrochlorothiazide 25 Gulf is indicated for:

- Oedema associated with congestive cardiac failure, hepatic cirrhosis and nephrotic syndrome
- As a therapeutic agent for its antidiuretic effect on patients with diabetes insipidus

- Essential hypertension, in combination with or without other antihypertensive agents.

4.2 Posology and method of administration

Posology

Therapy should be initiated at the lowest dose required to achieve desired effects. Treatment should be individualised.

Adults

Oedema

An initial dose of 25 mg to 100 mg is usually given, and later reduced to a smaller maintenance dose, often given on alternative days.

An initial dose of up to 200 mg may be necessary in some patients, but larger doses have no additional effect.

Hypertension

25 mg to100 mg daily in conjunction with a reduced dose of the hypotensive medicine.
The dosage should not be higher than necessary to achieve the desired effect. Prolonged treatment may result in potassium ion loss. Potassium supplements may be necessary (see section 4.4).

Paediatric population

2,5 mg per kg body mass daily, in two divided doses.

Method of administration

Oral.

The tablets must be swallowed with a drink of water and should be taken with or after meals to minimise gastrointestinal side effects.

4.3 Contraindications

Hydrochlorothiazide 25 Gulf is contraindicated in:

- Patients with hypersensitivity to hydrochlorothiazide, other sulfonamide-derived medicines or to any of the excipients in Hydrochlorothiazide 25 Gulf (see section 6.1)
- Patients with anuria or severe renal (creatinine clearance < 30 mL/min) impairment (see section 4.4)
- Patients with severe hepatic impairment (see section 4.4)
- Patients with Addison's disease
- Patients with pre-existing hypercalcaemia (see section 4.4)
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip (see section 4.4)
- The second and third trimesters of pregnancy and during lactation (see section 4.6)
- Concomitant administration with lithium (see section 4.5).

4.4 Special warnings and precautions for use

Hepatobiliary disorders

Hydrochlorothiazide 25 Gulf 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 and may increase the risk of hepatic encephalopathy (see section 4.3). Patients with hepatic cirrhosis are particularly at risk from hypokalaemia.

Renal and urinary disorders

Hydrochlorothiazide 25 Gulf should be given with caution in renal function impairment since the hypovolaemia produced by the medicine can trigger uraemia, thus further reducing renal function (see section 4.3).

In patients with renal disease, Hydrochlorothiazide 25 Gulf may precipitate azotaemia and oliguria. Cumulative effects of the medicine may develop in patients with impaired renal function. Hydrochlorothiazide 25 Gulf is ineffective at creatinine clearance values of 30 mL/min or below (i.e., moderate or severe renal insufficiency). If progressive renal impairment becomes evident, as indicated by rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

Hyperuricaemia

Hydrochlorothiazide 25 Gulf should be administered with caution to patients with gout or hyperuricemia, since the medicine reduces uric acid clearance. Hyperuricaemia may occur, or Hydrochlorothiazide 25 Gulf may precipitate attacks of acute gout in susceptible patients**.**
Cases of gout attacks have been reported at the start of a hydrochlorothiazide treatment. The dosage will be adapted based on the plasma concentrations of uric acid.

Diabetes mellitus

Hydrochlorothiazide 25 Gulf may cause hyperglycaemia and aggravate or unmask diabetes mellitus. Glucose tolerance is impaired by Hydrochlorothiazide 25 Gulf. Blood glucose concentrations should be monitored in patients taking antidiabetic medicines, including insulin and oral hypoglycaemic medicines, since requirements may change (see section 4.5).

Electrolyte imbalance

All patients should be carefully observed for signs of fluid and electrolyte imbalance e.g. hyponatraemia, hyperchloraemic alkalosis, hypokalaemia and hypomagnesaemia. Serum and urine electrolyte determinations are particularly important, especially in the presence of vomiting or during parenteral fluid therapy.

Warning signs or symptoms of fluid and electrolyte imbalance, 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 and vomiting.

Elderly patients are particularly susceptible to electrolyte imbalance.

Hypotension

When Hydrochlorothiazide 25 Gulf is administered with other diuretics or antihypertensives, additive effects are observed, which is used to increase its effectiveness. However, orthostatic hypotension may also occur, so it is necessary to adjust the doses appropriately to the needs of each patient.

Hypercalcaemia

Hydrochlorothiazide 25 Gulf should be used with caution in patients with hypercalcaemia as the urinary excretion of calcium can be reduced, sometimes resulting in mild hypercalcaemia. Hydrochlorothiazide 25 Gulf may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Hydrochlorothiazide 25 Gulf should be discontinued before carrying out tests for parathyroid function.

Hypokalaemia

Hypokalaemia may develop, especially with brisk diuresis when severe cirrhosis is present, in patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) also known as corticotropin, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalaemia. Hypokalaemia may cause cardiac dysrhythmia and may also sensitise or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalaemia may be avoided or treated by use of potassium sparing diuretics or potassium supplements such as foods with a high potassium content (see sections 4.5 and 4.8).

Chloride deficit

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Hyponatraemia

Dilutional hyponatraemia may occur in oedematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in less frequent instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypomagnesaemia

Thiazides, including Hydrochlorothiazide 25 Gulf, have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesaemia (see section 4.8).

Eye disorders

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

Sulfonamide or sulfonamide derivative medicines 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 medicine initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue medicine 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.

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), as in Hydrochlorothiazide 25 Gulf, exposure has been observed in two epidemiological studies.

Photosensitising actions of Hydrochlorothiazide 25 Gulf could act as a possible mechanism for NMSC.

Patients taking Hydrochlorothiazide 25 Gulf 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 to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies.

Hydrochlorothiazide 25 Gulf should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Systemic lupus erythematosus (SLE)

There is a possibility that Hydrochlorothiazide 25 Gulf may exacerbate or activate systemic lupus erythematosus in susceptible patients.

Antihypertensive medicines

Hydrochlorothiazide 25 Gulf may add to or potentiate the action of other antihypertensive medicines (see section 4.5).

Cholesterol and triglyceride levels

Increases in cholesterol and triglyceride levels may be associated with Hydrochlorothiazide 25 Gulf therapy.

Hypersensitivity reactions

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

Pancreatitis

Cases of pancreatitis have been reported in patients treated with hydrochlorothiazide as in Hydrochlorothiazide 25 Gulf (see section 4.8), so Hydrochlorothiazide 25 Gulf should be administered with caution to patients with a history of pancreatitis.

Lithium

Lithium should generally not be given with diuretics (see section 4.5).

Post-sympathectomy

The antihypertensive effects of Hydrochlorothiazide 25 Gulf may be enhanced in the post-sympathectomy patient.

Anti-doping test

Hydrochlorothiazide 25 Gulf could produce a positive analytical result in an anti-doping test.

Excipients

Lactose

Hydrochlorothiazide 25 Gulf contains lactose monohydrate thus patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this Hydrochlorothiazide 25 Gulf.

4.5 Interaction with other medicines and other forms of interaction

Calcium salts

Increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics such as Hydrochlorothiazide 25 Gulf.

Antidiabetic medicines (insulin and oral antidiabetics)

Hydrochlorothiazide 25 Gulf can increase blood sugar levels and interfere with diabetic control (see section 4.4). Dosage adjustment of the antidiabetic medicines may be necessary.

Digitalis glycosides

Hydrochlorothiazide 25 Gulf may enhance the toxicity of digitalis glycosides such as digoxin by depleting serum-potassium concentrations.

Non-depolarising skeletal muscle relaxants

Hydrochlorothiazide 25 Gulf may enhance the neuromuscular blocking action of competitive muscle relaxants, such as tubocurarine.

Antihypertensive medicines

Concomitant administration with other antihypertensive medicines (such as other diuretics, blood pressure lowering medicines, betablockers, nitrates, vasodilators) may intensify the antihypertensive efficacy of Hydrochlorothiazide 25 Gulf. When administered concurrently with ACE inhibitors (e.g. captopril, enalapril) severe first-dose hypotension and deterioration of renal function may develop. Therefore, diuretic therapy with Hydrochlorothiazide 25 Gulf 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.

Alcohol, barbiturates, phenothiazines, tricyclic antidepressants and opioids

Postural hypotension associated with Hydrochlorothiazide 25 Gulf may be enhanced by concomitant ingestion of alcohol, barbiturates, phenothiazines, tricyclic antidepressants or opioids due to the intensification of the antihypertensive efficacy of Hydrochlorothiazide 25 Gulf.

Medicines associated with potassium loss and hypokalaemia

The potassium-depleting effect of Hydrochlorothiazide 25 Gulf may be enhanced by medicines associated with potassium loss and hypokalaemia, e.g. kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH or corticotropin, carbenoxolone, stimulant laxatives, amphotericin B, penicillin G sodium, salicylic acid and derivatives, and beta2-agonists such as salbutamol. The monitoring of potassium level is advised. Use of such combinations requires caution.

Pressor amines

Hydrochlorothiazide 25 Gulf has been reported to diminish the response to pressor amines, such as noradrenaline and adrenalin, but the clinical significance of this effect is uncertain.

Lithium

Concomitant administration of Hydrochlorothiazide 25 Gulf and lithium is not generally recommended since Hydrochlorothiazide 25 Gulf may reduce the renal clearance of lithium and may lead to toxic blood concentrations of lithium (see sections 4.3 and 4.4).

Salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs) including selective COX-2 inhibitors

In some patients, the administration of salicylates and other NSAIDs can reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium- sparing and thiazide diuretics, such as Hydrochlorothiazide 25 Gulf. Therefore, when Hydrochlorothiazide 25 Gulf and salicylates or other NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

During simultaneous application of NSAIDs acute renal failure may occur in those patients, who develop hypovolaemia during hydrochlorothiazide therapy. Clinical observations suggest that the risk of hospitalisation is doubled in patients treated with NSAIDs and diuretics compared with those who only received diuretics. There are single cases of worsening of renal function, especially in patients with poor pre-existing renal function.

Hydrochlorothiazide may intensify the toxic effects of salicylates on the central nervous system.

Medicines associated with Torsades de Pointes

Because of the risk of hypokalaemia, caution should be used when Hydrochlorothiazide 25 Gulf is co-administered with medicines associated with Torsades de Pointes, e.g. anti-dysrhythmics [Class Ia anti-dysrhythmics (e.g. quinidine, hydroquinidine, disopyramide) and Class III anti-dysrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)], antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol) and other medicines (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastine, pentamidine, sparfloxacin, terfenadine, vincamine IV) known to induce Torsades de Pointes.

Colestyramine resin and colestipol

These medicines may delay or decrease absorption of hydrochlorothiazide, as in Hydrochlorothiazide 25 Gulf, by up to 84 % and 43 % respectively. Sulfonamide diuretics should be taken at least one hour before or four to six hours after these medicines.

Carbamazepine

Concomitant use of carbamazepine and hydrochlorothiazide, as in Hydrochlorothiazide 25 Gulf, has been associated with the risk of symptomatic hyponatraemia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used.

Metformin

Metformin should be used with caution owing to the risk of lactic acidosis induced by possible functional renal failure associated with hydrochlorothiazide, as in Hydrochlorothiazide 25 Gulf.

Allopurinol

Concomitant administration of thiazide diuretics, such as Hydrochlorothiazide 25 Gulf, can

increase the risk of hypersensitivity reactions to allopurinol.

Amantadine

Concomitant administration of thiazide diuretics can increase the risk of undesirable effects of amantadine by decreasing its tubular secretion.

Baclofen

Baclofen increased the antihypertensive effect of hydrochlorothiazide. Blood pressure and renal function should be monitored, and the dosage of the Hydrochlorothiazide 25 Gulf should be adapted.

Cytostatics (e.g. cyclophosphamide and methotrexate)

Concomitant administration of thiazide diuretics, such as Hydrochlorothiazide 25 Gulf, can reduce the renal excretion of cytostatics and increase the myelosuppressive effects.

Anticholinergics (e.g. atropine and biperiden)

The bioavailability of thiazide-like diuretics can be increased by anticholinergics, which is apparent as a result of a reduction in gastrointestinal motility and gastric emptying speed.

Quinidine

The clearance of quinidine can be reduced when hydrochlorothiazide and quinidine are given concomitantly.

Tetracyclines

The concomitant administration of hydrochlorothiazide and tetracyclines may cause an increase in serum urea.

Vitamin D

Co-administration of thiazide with vitamin D supplements may increase serum calcium levels due to decreased excretion of calcium.

Ciclosporin

Concomitant treatment with diuretics can increase the risk of hyperuricaemia and gout-like complications.

Betablockers and diazoxide

Thiazide diuretics, such as Hydrochlorothiazide 25 Gulf, can increase the hyperglycaemic effect of diazoxide and betablockers.

Methyldopa

In the literature, the occurrence of haemolytic anaemia has been reported with the concomitant use of hydrochlorothiazide and methyldopa.

Selective serotonin reuptake inhibitors

There is an increased risk of hyponatremia in concomitant therapy with SSRI's and diuretics such as thiazides and furosemide.

Laboratory tests

Because of its' effect on calcium metabolism, Hydrochlorothiazide 25 Gulf should be discontinued before carrying out tests for parathyroid function (see section 4.4).

Hydrochlorothiazide 25 Gulf may cause diagnostic interference of the bentiromide test.

Hydrochlorothiazide 25 Gulf may decrease serum Protein Bound Iodine (PBI) levels without signs of thyroid disturbance.

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals.

Iodine contrast medium

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before administration.

4.6 Fertility, pregnancy and lactation

Hydrochlorothiazide 25 Gulf is contraindicated in the second and third trimesters of pregnancy and during lactation (see section 4.3).

Pregnancy

There is limited experience with Hydrochlorothiazide 25 Gulf during pregnancy, especially during the first trimester. Hydrochlorothiazide 25 Gulf crosses the placenta barrier and appears in cord blood. There have been reports of neonatal jaundice, icterus, thrombocytopenia and electrolyte imbalances following maternal treatment. Reductions in maternal blood volume could also adversely affect placental perfusion.

Hydrochlorothiazide 25 Gulf should not be used for gestational oedema, gestational hypertension or pre-eclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide 25 Gulf should not be used for essential hypertension in pregnant women.

Breastfeeding

Hydrochlorothiazide 25 Gulf is distributed into breastmilk and is not recommended for use in

lactation. Hydrochlorothiazide 25 Gulf in high doses causing intense diuresis can inhibit the milk production.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

It is not always possible to predict to what extent Hydrochlorothiazide 25 Gulf may interfere with the daily activities of a patient. Hydrochlorothiazide 25 Gulf has a moderate influence on the ability to drive and use machines. Hydrochlorothiazide 25 Gulf can cause adverse effects such as dizziness, drowsiness and visual disturbance. When Hydrochlorothiazide 25 Gulf is taken with alcohol, barbiturates, phenothiazines, tricyclic antidepressants, opioids or other antihypertensives, it increases the risk of postural hypotension and may impair a patient's ability to drive or operate machinery (see section 4.5).

Patients should ensure that they do not drive, use machinery or perform any tasks that require concentration, until they are certain that Hydrochlorothiazide 25 Gulf does not adversely affect their ability to do so (see sections 4.4 and 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

Intrahepatic cholestatic jaundice, anorexia, hyperglycaemia, hyperuricaemia, gout and glycosuria are among the most frequent adverse effects of Hydrochlorothiazide 25 Gulf. The Stevens-Johnson and Lyell's syndromes (the latter is also known as toxic epidermal necrolysis (TEN)) have been reported.

b. Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Frequency unknown	sialadenitis
Neoplasm benign, malignant and unspecified (including cysts and polyps)	Frequency unknown	non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent	blood dyscrasias, thrombocytopenia, granulocytopenia, leukopenia, aplastic anaemia, haemolytic anaemia, increased cholesterol and triglyceride levels
	Frequency unknown	agranulocytosis, neutropenia, bone marrow depression
Immune system disorders	Less frequent	anaphylactic reactions
	Frequency unknown	purpura, hypersensitivity reactions
Metabolism and nutrition disorders*	Frequent	anorexia, hyperglycaemia, hyperuricaemia, gout

	Less frequent	electrolyte imbalances, hypochloraemic alkalosis, hyponatraemia, hypokalaemia
	Frequency unknown	hypomagnesaemia hypercalcemia
Psychiatric disorders	Less frequent	restlessness
	Frequency unknown	depression, sleep disturbances
Nervous system disorders	Less frequent	lethargy, drowsiness, seizures, headache, paraesthesia, dizziness
Eye disorders*	Less frequent	xanthopsia, transient blurred vision
	Frequency unknown	acute myopia and secondary acute angle-closure glaucoma, choroidal effusion
Ear and labyrinth disorders	Frequency unknown	vertigo
Cardiac disorders	Frequency unknown	cardiac dysrhythmias
Vascular disorders*	Less frequent	postural hypotension, necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders	Less frequent	pulmonary oedema, pneumonitis
	Frequency unknown	respiratory distress
Gastrointestinal disorders	Less frequent	dry mouth, gastric irritation, nausea, vomiting, constipation, diarrhoea, intestinal ulceration, pancreatitis
	Frequency unknown	gastrointestinal disturbances, cramping
Hepatobiliary disorders	Frequent	intrahepatic cholestatic jaundice
Skin and subcutaneous tissue disorders	Less frequent	rash, urticaria, photosensitivity reactions
	Frequency unknown	erythema multiforme including Stevens-Johnson Syndrome (SJS)*, exfoliative dermatitis including toxic epidermal necrolysis (TEN)*, Systemic lupus erythematosus (SLE), cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, alopecia

Musculoskeletal and connective tissue disorders	Less frequent	muscle pain and cramps, muscle spasm
Renal and urinary disorders	Frequent	glycosuria
	Less frequent	urinary excretion of calcium is reduced, oliguria
	Frequency unknown	renal failure, renal dysfunction, interstitial nephritis
Reproductive system and breast disorders	Less frequent	impotence
General disorders and administrative site conditions	Less frequent	thirst, weakness, fever

*See below section c for description of selected adverse reactions.

c. Description of selected adverse reactions

Eye disorders

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

Electrolyte and fluid imbalance and metabolic disorders

During long-term continuous therapy electrolyte- and fluid imbalance is frequently reported, especially hypokalaemia, hyponatraemia. Less frequently in long-term continuous therapy, hypomagnesaemia, hypochloraemia and hypercalcaemia may develop.

In higher doses loss of fluid and sodium due to enhanced diuresis may occur which may less frequently 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. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses in conjunction with restricted salt in the diet.

Excessive diuresis may lead to dehydration and hypovolaemia resulting in haemoconcentration and less frequently 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 dysrhythmias. Severe potassium loss may result in subileus or paralytic ileus or unconsciousness and coma. Hypokalaemia intensifies the effect of digitalis on cardiac muscle and administration of digitalis or its glycosides may have to be temporarily suspended and patients with cirrhosis of the liver are particularly at risk. Therefore, ECG disturbances and aggravated hypersensitivity of cardiac glycosides may occur.

Frequently hypermagnesuria develops, which only less frequently 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. Metabolic disturbances especially at high doses may occur, such as hyperglycaemia in diabetic and other susceptible patients, hyperuricaemia and precipitate attacks of gout in some patients, anorexia.

Vascular disorders

Postural hypotension (aggravated by barbiturates, phenothiazines, tricyclic antidepressants, alcohol, narcotics or antihypertensive medicines) (see section 4.5) and necrotising angiitis (vasculitis, cutaneous vasculitis) may occur.

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported to be life-threatening.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Alternately you can contact Gulf Drug Company (Pty) Ltd at +27 31 538 8700 or per info@gulfdrug.co.za.

4.9 Overdose

Symptoms and signs

Hydrochlorothiazide 25 Gulf can produce acute renal failure either from overdosage, producing saline depletion and hypovolaemia or, occasionally, as a result of a hypersensitivity reaction. The most frequent 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

dysrhythmias.

Treatment

In massive overdosage, treatment should be symptomatic, supportive and directed at fluid and electrolyte replacement. Dehydration, electrolyte imbalance, hepatic coma and hypotension should be corrected by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which Hydrochlorothiazide 25 Gulf is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 18.1 Diuretics

Pharmacotherapeutic group: Medicines acting on reno-urinary and genital system

ATC code: C03AA03

Mechanism of action

Hydrochlorothiazide is a diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium, potassium and chloride ions, and consequently of water. It also slightly increases bicarbonate excretion without appreciable alteration of the acid-base balance or the pH of the urine. It has a lowering effect on the blood pressure and enhances the action of other hypotensive medicine such as guanethidine, methyldopa and rauwolfia alkaloids.

5.2 Pharmacokinetic properties

Absorption

Hydrochlorothiazide is absorbed from the gastrointestinal tract, distributed throughout the extracellular space and diffuses across the placenta.

Distribution

Hydrochlorothiazide is distributed throughout the extracellular space and diffuses across the placenta.

Biotransformation

Diuresis occurs in about two hours, reaches a maximum in about four hours, and lasts for about twelve hours. Tolerance does not develop, and therapeutic efficacy is maintained when it is administered over long periods, but patients may not respond if their glomerular filtration rate is markedly reduced.

Elimination

The route of elimination is via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Crospovidone

Microcrystalline cellulose

Lactose anhydrous

Magnesium stearate

Pregelatinised starch

Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC/Al blister strips and HDPE/PP containers: 24 months or 36 months.

Patient ready packs (LDPE): 15 months.

6.4 Special precautions for storage

Store at or below 25 °C in a cool, dry place. Protect from light and moisture.

Keep HDPE/PP containers tightly closed.

Do not remove tablets from container/blister strips until required for use.

Do not remove tablets from patient ready packs until required for use.

6.5 Nature and contents of container

Clear, push-through PVC/Al blister strips of 10 or 14 tablets each, packed into a unit-carton containing 14, 28 or 30 tablets.

White plastic HDPE/PP containers of 28, 30, 100 or 500 tablets.

Printed patient ready LDPE packs of 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gulf Drug Company (Pty) Ltd

22 Burnside Drive

Old Mill Industrial Park

Mount Edgecombe

4300

8. REGISTRATION NUMBER

41/18.1/0559

9. DATE OF FIRST AUTHORISATION

11 June 2018.

10. DATE OF REVISION OF THE TEXT

05 August 2024.