Approved Professional Information for Medicines for Human Use:

RIDAFLO

1. NAME OF THE MEDICINE

RIDAFLO 12,5 tablets

RIDAFLO 25 tablets

RIDAFLO 50 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RIDAFLO 12,5:

Each tablet contains 12,5 mg hydrochlorothiazide.

RIDAFLO 25:

Each tablet contains 25 mg hydrochlorothiazide.

RIDAFLO 50:

Each tablet contains 50 mg hydrochlorothiazide.

Contains Sugar

RIDAFLO 12,5:

Each tablet contains 10 mg lactose monohydrate.

RIDAFLO 25:

Each tablet contains 20 mg lactose monohydrate.

RIDAFLO 50:

Each tablet contains 40 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

RIDAFLO 12,5:

White to off white, round shaped, flat face, beveled edge tablets debossed with “L” on one side and “7” on other side.

RIDAFLO 25:

White to off white, round shaped, biconvex tablets debossed with “J” on one side and “2” on other side.

RIDAFLO 50:

White to off white, round shaped, biconvex tablets debossed with “J 7” on one side and break line on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oedema due to sodium and water retention:

Paradoxically, hydrochlorothiazide appears to have an antidiuretic effect on patients with diabetes insipidus and may be of value in the management of the disease.

Essential hypertension:

Preferably in combination with reduced doses of specific anti-hypertensive medicines.

4.2 Posology and method of administration

Posology

If a single dose of RIDAFLO 12,5 mg is indicated, the dose should preferably be taken in the morning in order to minimise the effect of increased frequency of urination during sleep. RIDAFLO 12,5 mg should be taken with or after meals to minimise stomach upset.

Adults - For the treatment of oedema:

An initial dose of 25 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.

Adults – For the treatment of mild to moderate hypertension:

12,5 mg daily.

Adults - As an adjunct in the treatment of hypertension:

25 – 100 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.

Paediatric population

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

Method of administration

The tablet should be taken orally.

4.3 Contraindications

- Hypersensitivity to the hydrochlorothiazide or to any of the excipients listed in section 6.1.
- Patients with anuria or severe renal insufficiency (creatinine clearance < 30 mL/min).

- Patients with severe hepatic impairment.
- Patients with Addison's disease.
- Patients with pre-existing hypercalcaemia.
- The second and third trimesters of pregnancy and during lactation (see section 4.6).\
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Hepatic impairment:

RIDAFLO should be used with caution in patients with impaired hepatic function since they may increase the risk of hepatic encephalopathy. Patients with hepatic cirrhosis are particularly at risk from hypokalaemia.

Metabolic and endocrine effects:

Thiazide treatment as in RIDAFLO can alter glucose tolerance. In diabetic patients it may be necessary to adjust the dose of insulin or oral hypoglycaemic. During the administration of thiazides, latent diabetes mellitus may occur.

Cholesterol and triglyceride levels

Increases in cholesterol and triglyceride levels have been associated with treatment with thiazide diuretics. Hydrochlorothiazide should be administered with caution to patients with gout or hyperuricemia, since the medicine reduces uric acid clearance. 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.

Renal impairment:

Hydrochlorothiazide should be used with caution in patients with renal dysfunction because the hypovolemia produced by the medicine can trigger uremia, thus further reducing renal function.

Hyperuricaemia

Hyperuricaemia may occur or RIDAFLO may precipitate attacks of acute gout in susceptible patients.

Electrolyte imbalance:

All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid.

As in any patient who is receiving a diuretic treatment, a periodic determination of serum electrolytes should be made at appropriate intervals. The warning signs of an imbalance of fluids or electrolytes are dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, pain or muscle cramps, muscle fatigue, hypotension, oliguria, tachycardia and gastrointestinal disorders, such as nausea or vomiting.

Patients with serious electrolyte imbalances such as hyponatremia or hypokalaemia should correct such imbalances before starting a diuretic treatment with hydrochlorothiazide. Otherwise, these medicines can cause serious dysrhythmias, hypotension and seizures. The elderly, malnourished, polymedicated, cirrhotic and patients with heart failure are more likely to develop such reactions.

Hypercalcaemia

RIDAFLO may increase plasma calcium concentrations and should be used with caution in patients with hypercalcemia. High hypercalcaemia may indicate hidden hyperparathyroidism. Thiazide treatment should be discontinued before performing parathyroid function tests.

Hypomagnesaemia

It has been observed that thiazides increase urinary excretion of magnesium, which can lead to hypomagnesaemia.

Hypokalaemia

Hypokalaemia may develop, especially with brisk diuresis, in patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH) also known as corticotropin, of after

prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalaemia. Hypokalaemia may cause cardiac dysrhythmia and may also sensitize 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.

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.

Hyponatremia

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

Systemic lupus erythematosus (SLE)

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

Lithium

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

Acute myopia and secondary angle-closure glaucoma

RIDAFLO, a sulphonamide, can cause an idiosyncratic reaction, resulting in 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 medicine initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue RIDAFLO 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 sulphonamide or penicillin allergy.

Post-sympathectomy

The antihypertensive effects of RIDAFLO may be enhanced in the post-sympathectomy patient.

Anti-doping test:

The hydrochlorothiazide contained in RIDAFLO could give a positive test result.

Hypersensitivity reactions

Sensitivity reactions may occur in patients with and without a history of allergy or bronchial asthma.
RIDAFLO may exacerbate or activate systemic lupus erythematosus.
Cases of pancreatitis have been reported in patients treated with hydrochlorothiazide as in RIDAFLO, so RIDAFLO should be administered with caution to patients with a history of pancreatitis.
When RIDAFLO 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.
People over 65 may have a greater sensitivity to the diuretic effects of RIDAFLO. Elderly patients are particularly susceptible to electrolyte imbalance.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NSCLC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] has been observed with exposure to increasing cumulative doses of

hydrochlorothiazide (HCTZ) in two epidemiological studies. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking RIDAFLO should be informed of the risk of NMSC and advised to regularly check their skin for new lesions and promptly report any suspicious skin lesions. Possible preventative measures such as limited exposure to sunlight and UV rays and, in the case of exposure, adequate protection should be advised to the patients to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. RIDAFLO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin or lip (see section 4.3).

Excipients: lactose intolerance

RIDAFLO contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take RIDAFLO.

4.5 Interaction with other medicines and other forms of interaction

Antidiabetic medicines (oral medicines or insulin):

Thiazide diuretics, as in RIDAFLO reduce insulin sensitivity increasing glucose intolerance and hyperglycaemia. Therefore, diabetic patients who start a hydrochlorothiazide treatment, as in RIDAFLO should carefully monitor their blood glucose levels and properly adjust the doses of antidiabetics.

Baclofen:

Baclofen increased antihypertensive effect. Blood pressure and renal function should be monitored and the dosage of the antihypertensive will be adapted.

Other Antihypertensives:

Concomitant use with RIDAFLO produces an additive effect, increasing the hypotensive effect.

IECAS:

Possible potentiation of toxicity with the presence of hypokalemia.

Cholestyramine and colestipol resins:

The absorption of hydrochlorothiazide decreases or is delayed in the presence of ion exchange resins. Single doses of cholestyramine or colestipol fix hydrochlorothiazide, as in RIDAFLO and reduce its gastrointestinal absorption up to 85 % and 43 %, respectively. It is recommended to administer thiazides at least 4 hours before cholestyramine. The same goes for colestipol, although to a lesser extent, so it is recommended to administer thiazides at least 2 hours before.

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH), beta2-agonists or carbenoxolone or stimulant laxatives:

RIDAFLO may intensify electrolyte disturbance, especially hypokalemia. Concomitant use of hydrochlorothiazide with amiloride, spironolactone or triamterene may reduce the risk of hypokalaemia, due to its potassium-sparing effects. The use of these medicines may be an alternative to potassium supplements that are recommended for patients treated with diuretics. The risk of hydrochlorothiazide-induced hypokalemia is higher if it is administered concomitantly with other medicines that also reduce plasma potassium levels such as corticosteroids (corticotropin, amphotericin B), $beta_2$-agonists such as salbutamol or carbenoxolone. In these cases it is recommended to monitor potassium levels and cardiac function, adding if necessary potassium supplements.

Pressing amines (for example, epinephrine /adrenaline):

RIDAFLO may decrease the response to pressor amines, such as (norepinephrine /noradrenaline) but not enough to prevent its use.

Non-depolarizing muscle relaxants (eg, tubocurarine):

RIDAFLO may enhance the neuromuscular blocking action of competitive muscle relaxants such as turbocurarine.

Lithium:

Concomitant administration of RIDAFLO and lithium is not generally recommended since the association may lead to toxic blood concentrations of lithium. Although diuretics are sometimes used to counteract the polyuria caused by lithium, plasma levels must be monitored and doses adjusted (reduce lithium dose to 50 %) when combined with the diuretic.

Nonsteroidal anti-inflammatory drugs (indomethacin):

Inhibition of renal synthesis of prostaglandins produced by nonsteroidal anti-inflammatory drugs may reduce the diuretic, natriuretic and antihypertensive effects of RIDAFLO. It can also increase the risk of kidney failure, by reducing renal blood flow. Careful monitoring of these patients is recommended to check for any change in the effectiveness of diuretic treatment or any symptoms of renal impairment and if necessary hydrate the patient.

Calcium salts:

An increase in serum calcium levels may occur due to a decrease in urinary excretion, when administered concomitantly with thiazide diuretics as in RIDAFLO, which may cause hypercalcemia.

Cardiac glycosides:

Increases the possibility of digitalis toxicity (digoxin), associated with thiazide-induced hypokalemia.

Medicines associated with Torsades de pointes (sultopride):

Due to the risk of hypokalemia, caution should be used when administering RIDAFLO with medicines associated with torsades de pointes, e.g., some antiarrhythmics (eg: quinidine, hydroquinidine, disopyridine, amiodarone, sotalol, dofetilide, ibutilide), some antipsychotics (eg, thioridazine,

clopromazine, levomepromazine, sulpiride, haloperidol) and other medications known to induce Torsades de Pointes (eg: Ketanserin, mizolastin, vincamine, cisapride, erythromycin iv).

Carbamazepine:

The concomitant use of carbamazepine and hydrochlorothiazide as in RIDAFLO has been associated with the risk of symptomatic hyponatremia. The level of electrolytes should be controlled during this concomitant administration. If possible, another class of diuretic should be administered.

Ciclosporin

Concomitant treatment with ciclosporin may increase the risk of hyperuricemia and gouty complications.

Tetracyclines:

The concomitant administration of tetracyclines and thiazide diuretics increases the risk of increased urea induced by tetracyclines. This interaction is probably not applicable to doxycycline.

Anticholinergic medicines (eg atropine, biperidene):

The bioavailability of thiazide diuretics may increase with anticholinergic medicines, due to a decrease in gastrointestinal motility and the rate of stomach emptying.

Medicines used for the treatment of gout (probenecid, sulfinpyrazone and allopurinol):

A dosage adjustment of uricosuric medication may be necessary since hydrochlorothiazide as in RIDAFLO may raise the level of serum uric acid. It may be necessary to increase the dose of probenecid or sulfinpyrazone. Concomitant administration of thiazide diuretics, including RIDAFLO, may increase the incidence of allopurinol hypersensitivity reactions.

Beta blockers and diazoxide:

The concomitant use of thiazide diuretics, including hydrochlorothiazide as in RIDAFLO, with beta blockers may increase the risk of hyperglycemia. Thiazide diuretics, including RIDAFLO, may increase the hyperglycemic effect of diazoxide.

Methyldopa:

Isolated cases of hemolytic anemia have been reported in patients who received concomitant treatment with hydrochlorothiazide as in RIDAFLO and methyldopa.

Amantadine:

Thiazides, including RIDAFLO, may increase the risk of adverse effects due to amantadine due to decreased tubular secretion.

Cytotoxic medicines (eg cyclophosphamide, methotrexate):

Thiazides, including RIDAFLO, can reduce renal excretion of cytotoxic medicines and enhance their myelosuppressive effects.

Salicylates

In case of high doses of salicylates, RIDAFLO may potentiate the toxic effect of salicylates on the central nervous system. They can also produce hypokalemia.

Antihypertensive medicines, alcohol, barbiturates, narcotics or antidepressants and opioids:

RIDAFLO may enhance the effect of other antihypertensive medicines, while postural hypotension associated with this therapy may be enhanced by concomitant ingestion of alcohol, barbiturates, or opioids. Diuretic therapy with RIDAFLO 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.

Other interactions:

Thiazide diuretics, including RIDAFLO may increase the photosensitizing effects of some medicines such as griseofulvin, phenothiazines, sulfonamides and sulfonylureas, tetracyclines, retinoids and medicines used in photodynamic therapy.

Laboratory tests:

RIDAFLO may cause analytical interference in the diagnosis of the bentiromide test. RIDAFLO may decrease serum Protein Bound Iodine (PBI) levels without signs of thyroid disturbance.

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function.

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

The safety of RIDAFLO in pregnancy and lactation has not been established.

Pregnancy

There is limited experience on the use of hydrochlorothiazide as in RIDAFLO during pregnancy.

Breastfeeding

Hydrochlorothiazide is excreted in breastmilk and is not recommended for use in breastfeeding.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

RIDAFLO can cause headache and dizziness, drowsiness and visual disturbance.

Patients should not drive, use machinery, or perform any tasks that require concentration until they are certain that RIDAFLO does not adversely affect their ability to do so.

4.8 Undesirable effects

Adverse effects of RIDAFLO are rare (< 10 %) and are generally dose-related, and can be minimized by establishing the minimum effective dose, particularly in arterial hypertension.

a) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with hydrochlorothiazide.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		Sialadenitis	
Neoplasm benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders		Aplastic anaemia, haemolytic anaemia, leukopenia, purpura,	Agranulocytosis, neutropenia, bone marrow

		thrombocytopenia, blood dyscrasias	depression
Immune system disorders		Hypersensitivity reactions	Anaphylactic reactions, purpura
Metabolism and nutrition disorders	Electrolyte imbalances, Hypochloraemic alkalosis, 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), and hypokalaemia (intensifies the effect of digitalis on cardiac muscle and administration of digitalis or its glycosides may have to be temporarily suspended)	Metabolic disturbances especially at high doses, hyperglycaemia and carbohydrate intolerance in diabetic and other susceptible patients, asymptomatic hyperuricaemia and precipitate attacks of gout in some patients, hypomagnesaemia, anorexia hypokalaemia, electrolyte imbalance (hyponatraemia, hypochloraemia, metabolic alkalosis, hypercalcaemia and	

		hypokalaemia), increased cholesterol and triglycerides.	
Psychiatric disorders	Restlessness	Agitation, depression, sleep disorders.	
Nervous system disorders	Lethargy, drowsiness, seizures	Loss of appetite, paraesthesia, dizziness, vertigo, headache, weakness, restlessness.	Light-headedness
Eye disorders		xhantopsia (yellow vision)	Transient blurred vision, choroidal effusion
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		allergic myocarditis, vasculitis	Cardiac dysrhythmias
Vascular disorders		Postural hypotension (aggravated by barbiturates, alcohol or narcotics)	Necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders		Respiratory disorders including pneumonitis, pulmonary oedema.	Respiratory distress
Gastrointestinal disorders	Gastrointestinal disturbances, dry mouth	Gastric irritation, nausea, vomiting, constipation, diarrhoea, intestinal ulceration has occurred following the administration of tablets containing thiazides with an enteric-coated core of potassium chloride, pancreatitis, cramping	
Hepatobiliary disorders		Intrahepatic cholestatic jaundice.	
Skin and subcutaneous tissue disorders		Photosensitivity reactions, rash,	Erythema multiforme including Stevens-Johnson

			Syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria
Musculoskeletal and connective tissue disorders	Muscle pain and cramps	Muscle spasm	
Renal and urinary disorders	Oliguria	Renal function disorders, interstitial nephritis, polyuria, polaquiuria, glycosuria, urinary excretion of calcium is reduced	Renal failure, renal dysfunction, interstitial nephritis

Reproductive system and breast disorders		Impotence	
General disorders and administration site conditions	Thirst, weakness		Fever

b) 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of RIDAFLO 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

4.9 Overdose

Symptoms

RIDAFLO 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. In cases of recent ingestion emesis or gastric lavage should be carried out. 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 RIDAFLO is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 18.1 – Diuretics.

Pharmacotherapeutic group: Diuretics

ATC Code: C03AA03

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 medicines 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 synthesis is via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Maize starch

Methylhydroxyethylcellulose

Microcrystalline cellulose

Purified water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Store in original packaging to protect it from light.

6.5 Nature and contents of container

RIDAFLO is packed in clear PVC / aluminium blister packs. The blisters are subsequently packed into cardboard boxes.

Pack sizes: 28's, 30's, 56's, 84's, 100's and 112's tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

RIDAFLO 12,5: 56/18.1/0220

RIDAFLO 25: 56/18.1/0221

RIDAFLO 50: 56/18.1/0222

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 September 2023

10. DATE OF REVISION OF THE TEXT