SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE
ADCO RETIC, 5 mg/50 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet of ADCO RETIC contains 5 mg amiloride as amiloride hydrochloride and 50 mg hydrochlorothiazide.

Contains sugar: lactose monohydrate 7,62 mg per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablets.

Peach coloured, diamond-shaped tablet with 'ACDO' embossed on one side and a break line on either side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
ADCO RETIC is indicated in the treatment of patients with:
- oedema of cardiac decompensation or associated with hepatic cirrhosis and corticosteroid therapy.
- essential hypertension. ADCO RETIC may be used alone or as an adjunct to other antihypertensive medicines.

4.2 Posology and method of administration
Posology
Potassium supplements should not be given with ADCO RETIC tablets.

Oedema
The usual dosage is one or two tablets a day. The optimal dosage is determined by the diuretic response and the serum potassium level. Once an initial diuresis has been achieved, reduction in dosage should be attempted for maintenance therapy.

Hypertension
The usual dosage is one ADCO RETIC tablet daily. Some patients may require half a tablet daily. ADCO RETIC may be used alone or as an adjunct to other antihypertensive medicines.

ADCO RETIC may add to or potentiate the action of other antihypertensive medicines. If

ADCO RETIC is added to therapy with other antihypertensive medicines, dosage reduction of such medicines may be necessary in order to reduce the risk of an excessive drop in blood pressure.

Special populations

Paediatric population

The safety of the use of amiloride hydrochloride (as in ADCO RETIC) in children has not been established (see section 4.3).

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to amiloride hydrochloride and hydrochlorothiazide or to any of the excipients listed in section 6.1.
- Concomitant use with spironolactone or triamterene.
- Severe hepatic failure.
- Addison's disease.
- Hypercalcaemia.
- Concurrent lithium therapy.
- Hyperkalaemia:
- ADCO RETIC should not be used in the presence of elevated plasma potassium levels (interpreted as over 5,5 mmol/L).
- Antikaliuretic therapy, potassium supplementation or potassium-rich food (except in severe and/or refractory cases of hypokalaemia under careful monitoring):
- Other antikaliuretic medicines and potassium supplements are contraindicated in patients receiving ADCO RETIC due to the potassium-sparing effect of amiloride hydrochloride (such combination therapy is commonly associated with rapid increases in plasma potassium levels).
- Impaired renal function:
- Anuria, acute renal failure, severe progressive renal disease and diabetic nephropathy are contraindications to the use of ADCO RETIC. Patients with increases in blood urea nitrogen (BUN) over 5 mmol/L, in serum creatinine levels over 130 µmol/L, or in whole blood urea values over 10 mmol/L should not receive ADCO RETIC without careful, frequent monitoring of serum electrolytes and BUN levels. Potassium retention in the presence of renal impairment is accentuated by the addition of an antikaliuretic medicine and may result in the rapid development of hyperkalaemia.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- In children:
- The safety of the use of amiloride hydrochloride in children has not been established; therefore, ADCO RETIC is not recommended in children under 18 years of age.
- Contraindicated in pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

An increased risk of nonmelanoma 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. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking ADCO RETIC 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 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. ADCO RETIC 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).

Patients with partial heart block may develop complete heart block.

Rises in blood urea nitrogen concentrations may occur, as well as abnormalities in liver function tests.

Amiloride hydrochloride (as in ADCO RETIC) may cause hepatic encephalopathy manifested by tremors, confusion and coma. Patients with liver disease should be observed for this complication when ADCO RETIC is administered. In cirrhotic patients, jaundice associated with the underlying disease process may deepen.

In diabetic patients, hyperkalaemia may occur with amiloride hydrochloride (as in ADCO RETIC) administration, particularly if chronic renal disease or pre-renal azotaemia is present. Before initiating therapy in diabetic or suspected diabetic patients, the renal function status should be known. Therapy with ADCO RETIC should be discontinued at least three days before giving a glucose tolerance test.

Amiloride hydrochloride (as in ADCO RETIC**)** should be given with care to patients likely to develop acidosis, such as severely ill patients with cardiopulmonary disease and with decompensated diabetes.

Pathological changes in the parathyroid gland with hypercalcaemia and hypophosphatemia may occur with prolonged treatment with hydrochlorothiazide (as in ADCO RETIC).

Hydrochlorothiazide (as in ADCO RETIC) should be used with caution in patients with impaired hepatic or renal function, or with diabetes mellitus or adrenal disease. Insulin requirements in diabetic patients may be increased, decreased, or unchanged due to hydrochlorothiazide. Diabetes mellitus which has been latent may become manifest during thiazide administration. Blood-glucose concentrations should be monitored in patients taking antidiabetic medicines since their requirements of these medicines may change.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Electrolyte imbalance and reversible BUN increases:
Hydrochlorothiazide (as in ADCO RETIC) may produce hypomagnesaemia, hyponatraemia, hypochloraemia and hypokalaemia. Hyponatraemia may occur in patients with congestive heart failure who are very oedematous, particularly with large doses in conjunction with restricted salt in the diet. Hypokalaemia intensifies the effect of digoxin on cardiac muscle and administration of digoxin or its glycosides may have to be temporarily suspended. Urinary calcium excretion may be decreased in patients receiving hydrochlorothiazide (as in ADCO RETIC). All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy.

If increasing azotaemia and oliguria occur during treatment ADCO RETIC tablets should be discontinued.

Hydrochlorothiazide (as in ADCO RETIC) may interfere with a number of diagnostic tests, including tests for parathyroid function; serum concentrations of protein-bound iodine may increase without signs of thyroid disturbance. ADCO RETIC should be discontinued before carrying out tests for parathyroid function.

Effects related to diuresis in cirrhotic patients:
Oral diuretic therapy is more frequently accompanied by adverse reactions in patients with hepatic cirrhosis and ascites because these patients are intolerant of acute shifts in electrolyte balance, and because they often have pre-existing hypokalaemia as a result of associated aldosteronism.

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

The possibility of exacerbation or activation of systemic lupus erythematosus may occur.

Patients should be observed regularly for the possible occurrence of liver dysfunction, idiosyncratic reactions, or blood dyscrasias.

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

Sulphonamide or sulphonamide 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the 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 sulphonamide or penicillin allergy.

Excipients
ADCO RETIC contains lactose monohydrate. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take ADCO RETIC.

ADCO RETIC contains the colourant Sunset yellow FCF lake which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction
Lithium
Lithium should generally not be given to patients receiving diuretics (such as ADCO RETIC) since the risk of lithium toxicity is very high in such patients due to the decrease in renal clearance of lithium.

Non-steroidal anti-inflammatory medicines including selective cyclooxygenase-2 (COX-2) inhibitors
Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of antihypertensive drugs, including the diuretic, natriuretic and antihypertensive effects of diuretics (such as ADCO RETIC).

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory medicines, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Concomitant administration of NSAIDs and potassium-sparing medicines, including amiloride hydrochloride, may cause hyperkalaemia, particularly in elderly patients. Therefore, when amiloride hydrochloride is used concomitantly with NSAIDs, serum potassium levels should be carefully monitored.

Amiloride hydrochloride
When amiloride hydrochloride is administered concomitantly with an angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, trilostane, ciclosporin or tacrolimus, the

risk of hyperkalaemia may be increased. Therefore, if concomitant use of these medicines is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Hydrochlorothiazide
When given concurrently, the following medicines may interact with thiazide diuretics (as in ADCO RETIC):

The potassium depleting effects of hydrochlorothiazide (as in ADCO RETIC) may be enhanced by corticosteroids, corticotrophin and carbenoxalone.

Hydrochlorothiazide (as in ADCO RETIC) potentiates the action of other antihypertensive medicines. Therefore, the dosage of these medicines, especially the ganglion blockers, may need to be reduced when ADCO RETIC tablets are added to the regimen. 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.

Hydrochlorothiazide (as in ADCO RETIC) may increase the neuromuscular blocking action of non-depolarising muscle relaxants like tubocurarine. The antihypertensive effect of ADCO RETIC tablets may be enhanced in the post sympathectomy patient.

Hydrochlorothiazide (as in ADCO RETIC) may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude the effectiveness of the pressor agent for therapeutic use.

Orthostatic hypotension due to hydrochlorothiazide (as in ADCO RETIC) may be potentiated by alcohol, barbiturates or narcotics.

Oral and parenteral antidiabetic medicines may require adjustment of dosage with concurrent use. ADCO RETIC can act synergistically with chlorpropamide to increase the risk of hyponatraemia.

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 %, respectively. When cholestyramine is given 4 hours after the hydrochlorothiazide, the absorption of hydrochlorothiazide is reduced by 30 to 35 %.

4.6 Fertility, pregnancy and lactation
ADCO RETIC is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy
Diuretics
The routine use of diuretics in otherwise healthy pregnant women with or without mild

oedema is not indicated, because they may be associated with hypovolaemia, increased blood viscosity, and decreased placental perfusion. Diuretics do not prevent the development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful for its treatment.

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance, bone marrow depression and thrombocytopenia.

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

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breastfeeding
Although it is not known whether amiloride hydrochloride is excreted in human milk, it is known that hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of ADCO RETIC during breast feeding is not recommended. If ADCO RETIC is used during breastfeeding, doses should be kept as low as possible.

Fertility
No data available.

4.7 Effects on ability to drive and use machines
Patients may experience weakness, fatigue, dizziness, stupor and vertigo. Should any of these occur, the patient should be cautioned not to drive or operate machinery.

4.8 Undesirable effects
Tabulated list of adverse effects
Adverse effects of ADCO RETIC

System Organ Class	Frequency	Adverse effects
Metabolism and nutrition disorders	Frequency unknown	Electrolyte imbalance, hyponatraemia (see section 4.4), dehydration, symptomatic hyponatraemia
Psychiatric disorders	Frequency unknown	Insomnia, nervousness, depression, sleepiness

Nervous system disorders	Frequency unknown	Stupor
Cardiac disorders	Frequency unknown	Dysrhythmia, tachycardia, angina pectoris
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dyspnoea, nasal congestion
Gastrointestinal disorders	Frequency unknown	Anorexia, nausea, vomiting, diarrhoea or constipation, appetite changes, abdominal fullness, flatulence, hiccups, bad taste
Skin and subcutaneous tissue disorders	Frequency unknown	Flushing, diaphoresis
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Leg ache, joint pain, back pain
Renal and urinary disorders	Frequency unknown	Dysuria, nocturia, incontinence, renal dysfunction including renal failure
Reproductive system and breast disorders	Frequency unknown	Impotence
General disorders and administrative site conditions	Frequency unknown	Malaise, chest pain, syncope

Adverse effects of amiloride

System Organ Class	**Frequency**	**Adverse effects**
Blood and lymphatic system disorders	Frequency unknown	Aplastic anaemia, neutropenia
Metabolism and nutrition disorders	Frequency unknown	Elevated serum potassium levels (> 5,5 mmol/L)
Psychiatric disorders	Frequency unknown	Confusion, minor psychiatric changes, decreased libido, somnolence
Nervous system disorders	Frequency unknown	Dizziness, weakness, vertigo, paraesthesia, tremors, encephalopathy
Eye disorders	Frequency unknown	Visual disturbances, increased intra-ocular pressure
Ear and labyrinth disorders	Frequency unknown	Tinnitus
Cardiac disorders	Frequency unknown	Orthostatic hypotension, heart block, palpitation
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough

Gastrointestinal disorders	Frequency unknown	Activation of peptic ulcer, nausea, vomiting, diarrhoea, constipation, abdominal pain, thirst, gastrointestinal bleeding, dry mouth, dyspepsia
Hepato-biliary disorders	Frequency unknown	Abnormal liver function, jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Skin rash, pruritus, alopecia
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscle cramps, neck/shoulder ache, pain in extremities
Renal and urinary disorders	Frequency unknown	Polyuria, urinary frequency, bladder spasm

Adverse effects of hydrochlorothiazide

System Organ Class	**Frequency**	**Adverse effects**
Infections and Infestations	Frequency unknown	Sialadenitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequency unknown	Nonmelanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	Frequency unknown	Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia
Endocrine disorders	Frequency unknown	Hyperparathyroidism
Metabolism and nutrition disorders	Frequency unknown	Glycosuria, hyperglycaemia, hyperuricaemia, gout, hypokalaemia
Psychiatric disorders	Frequency unknown	Headache, restlessness, mental confusion
Nervous system disorders	Frequency unknown	Dizziness, vertigo, paraesthesia
Eye disorders	Frequency unknown	Transient blurred vision, xanthopsia, choroidal effusion
Cardiac disorders	Frequency unknown	Orthostatic hypotension, digoxin toxicity
Vascular disorders	Frequency unknown	Necrotizing angiitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Less frequent	Acute respiratory distress syndrome (ARDS) (see section 4.4)
	Frequency unknown	Respiratory distress including pneumonitis, pulmonary oedema
Gastrointestinal disorders	Frequency unknown	Pancreatitis, thirst, cramping, gastric irritation
Hepato-biliary disorders	Frequency unknown	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Frequency unknown	Anaphylactic-type reactions, Stevens-Johnson syndrome (erythema multiforme), urticaria,

		rash, pruritus, photosensitivity toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscle cramps
Renal and urinary disorders	Frequency unknown	Interstitial nephritis
General disorders and administrative site conditions	Frequency unknown	Fever, weakness, fatigue
Investigations	Frequency unknown	Changes in serum lipids

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Symptoms
See section 4.8 and section 4.4.
Treatment
Treatment is symptomatic and supportive.
Empty the stomach by emesis and give symptomatic treatment. Restore fluid and acid-base balance as indicated.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: A 18.1 Diuretics.
Diuretic and potassium-sparing agent, ATC code: C03EA01

ADCO RETIC tablets have diuretic and antihypertensive effects, combining the natriuretic action of hydrochlorothiazide, with the potassium conserving property of amiloride hydrochloride. The mild diuretic action of amiloride hydrochloride is additive to the natriuretic and diuretic activity of the thiazide.

5.2 Pharmacokinetic properties
About 70 % of an oral dose of hydrochlorothiazide is absorbed. It has a plasma half-life of 5.6 to 14.8 hours. It is excreted unchanged in the urine. It crosses the placental barrier and is secreted in breast milk.

About 50 % of an oral dose of amiloride hydrochloride is absorbed. It has a plasma half-life of about 6 to 9 hours, but its effects may persist for up to 48 hours after a single dose. It is

excreted unchanged in the urine and faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica
Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Pregelatinized starch
Stearic acid
Sunset yellow FCF lake (CI 15985)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Polypropylene securitainer and HDPE containers: 36 months
Glass bottles: 24 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

ADCO RETIC tablets are supplied in:

- white polypropylene securitainer bottles of 28, 30 and 100 fitted with white LDPE closures.
- a white polypropylene securitainer bottle of 1000 tablets fitted with a white MDPE closures.
- white cylindrical screw type HDPE containers of 100 and 1000 tablets with HDPE screw caps.
- soda glass type III amber glass vials of 30 tablets fitted with a white low density polyethylene snap-cap.
- amber glass vials of 100 and 1000 tablets fitted with a white polypropylene screw cap.

Not all pack types and pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)
V/18.1/260

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24 October 1988

10. DATE OF REVISION OF THE TEXT
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