PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AMILORETIC, 5 mg/ 50 mg tablets

AMILORETIC H.S. TABLETS, 2,5 mg/ 25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of AMILORETIC contains 5 mg amiloride hydrochloride and 50 mg hydrochlorothiazide.

Contains sugar: Lactose monohydrate 96,00 mg

Each tablet of AMILORETIC H.S.TABLETS contains 2,5 mg amiloride hydrochloride and 25 mg hydrochlorothiazide.

Contains sugar: Lactose monohydrate 48,00 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

AMILORETIC is a round, flat, pale peach, bevelled edged tablet, bisected on one side and engraved with a mortar and pestle on the other side.

AMILORETIC H.S.TABLETS is a round, flat, pale-peach, bisected tablet with bevelled edges imprinted with a mortar and pestle.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMILORETIC is indicated for:

- Oedema of cardiac decompensation or associated with hepatic cirrhosis and corticosteroid therapy.
- Essential hypertension.

AMILORETIC may be used alone or as an adjunct to other antihypertensive medicines.

4.2 Posology and method of administration

Posology

Adults

AMILORETIC: One tablet daily

AMILORETIC H.S. TABLETS: One to two tablets daily

Special populations

Elderly population

Particular caution is needed in the elderly because of their susceptibility to electrolyte imbalance; the dosage should be carefully adjusted to renal function and clinical response.

Renal impairment

Renal function should be monitored because the use of AMILORETIC in impaired renal function may result in the rapid development of hyperkalaemia. Thiazide diuretics become ineffective when creatinine levels fall below 30 mL/min (see section 4.4).

Hepatic impairment

AMILORETIC should be used with caution in patients with impaired hepatic function or progressive liver disease (see section 4.3), since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Paediatric population

The safety and efficacy of AMILORETIC in children under 18 years has not been established (see section 4.3).

Method of administration

For oral administration.

4.3 Contraindications

AMILORETIC is contraindicated in:

- Patients with a hypersensitivity to hydrochlorothiazide, amiloride or to any of the excipients in AMILORETIC (see section 6.1).
- Severe progressive renal disease.
- Severe hepatic failure.
- Patients with hyperkalaemia.

- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- Safety in pregnancy, lactation and childhood has not been established.
- Concomitant use with other potassium-conserving diuretics.
- Potassium supplements or potassium-rich food (except in severe and/or refractory cases of hypokalaemia under careful monitoring).
- Concomitant use with spironolactone or triamterene.
- Anuria; acute renal failure.
- Precoma associated with hepatic cirrhosis,
- Addison's disease.
- Hypercalcaemia.
- Concurrent lithium therapy.
- Diabetic nephropathy.
- Patients with blood urea over 10 mmol/L.
- Patients with diabetes mellitus, or those with serum creatinine over 130 µmol/L in whom serum electrolyte and blood urea levels cannot be monitored carefully and frequently.
- Children under 18 years of age.

4.4 Special warnings and precautions for use

Hyperkalaemia

Hyperkalaemia has been observed in patients receiving amiloride hydrochloride, either alone or with other diuretics, particularly in the aged or in hospital patients with hepatic cirrhosis or congestive heart failure with renal involvement, who were seriously ill, or were undergoing vigorous diuretic therapy. Such patients should be carefully observed for clinical, laboratory, and ECG evidence of hyperkalaemia (not always associated with an abnormal ECG). It should be given with care to patients likely to develop acidosis.

Neither potassium supplements nor a potassium-rich diet should be used with AMILORETIC except under careful monitoring in severe and/or refractory cases of hypokalaemia.

Some deaths have been reported in this group of patients.

Treatment of hyperkalaemia

Should hyperkalaemia develop, discontinue treatment immediately and, if necessary, take active measures to reduce the plasma potassium to normal.

Electrolyte imbalance

Although the likelihood of electrolyte imbalance is reduced by AMILORETIC, careful check should be kept for such signs of fluid and electrolyte imbalance as hyponatraemia, hypochloremic alkalosis, hypokalaemia and hypomagnesaemia. It is particularly important to make serum and urine electrolyte determinations when the patient is vomiting excessively or receiving parenteral fluids.

Hypomagnesaemia has also occurred. There is some evidence to suggest that electrolyte imbalances during long-term treatment with thiazides may be associated with an increased incidence of cardiac dysrhythmias. Adverse changes in plasma lipids have also been noted, but their clinical significance is unclear.

Warning signs or symptoms of fluid or electrolyte imbalance include: dryness of the mouth, weakness, lethargy, drowsiness, restlessness, seizures, confusion, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastro-intestinal disturbances such as nausea and vomiting.

Hypokalaemia may develop, especially as a result of brisk diuresis, after prolonged therapy or when severe cirrhosis is present. Hypokalaemia can sensitise or exaggerate the response of the heart to the toxic effects of digoxin (e.g., increased ventricular irritability).

Diuretic-induced hyponatraemia is usually mild and asymptomatic. It may become severe and symptomatic in a few patients with severe congestive heart failure who are very oedematous, particularly with large doses in conjunction with restricted salt in the diet.

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

Impaired Renal Function

When creatinine clearance falls below 30 ml/min, thiazide diuretics are ineffective. Patients with increases in blood urea over 5 mmol/l, with serum creatinine levels over 130 micromol/L, or with whole blood urea values over 10 mmol/l, or with diabetes mellitus should not receive AMILORETIC without careful, frequent monitoring of serum electrolytes and blood urea nitrogen 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.

Hepatic Disease

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

Azotaemia

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the medicine may develop in patients with impaired renal function. If increasing azotaemia and oliguria develop during treatment of renal disease, AMILORETIC should be discontinued. Blood-urea-nitrogen should be estimated periodically.

Metabolic

Hyperuricaemia may occur, or gout may be precipitated or aggravated, in certain patients receiving thiazides. Thiazides may impair glucose tolerance. Diabetes mellitus may be precipitated or aggravated by therapy with AMILORETIC (see section 4.3). Dosage adjustment of antidiabetic medicines, including insulin, may be required.

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

To minimise the risk of hyperkalaemia in diabetic or suspected diabetic patients, the status of renal function should be determined before initiating therapy with AMILORETIC. Therapy should be discontinued at least three days before giving a glucose tolerance test. Potassium-conserving therapy should be initiated only with caution in severely ill patients in whom metabolic or respiratory acidosis may occur, e.g., patients with cardiopulmonary disease or patients with inadequately controlled diabetes. Serum electrolytes should be estimated periodically.

Shifts in acid-base balance alter the balance of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in plasma potassium.

Sensitivity reactions

The possibility that thiazides may activate or exacerbate systemic lupus erythematosus in susceptible patients has been reported.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with increasing cumulative dose of hydrochlorothiazide

(HCTZ) exposure has been observed in two epidemiological studies. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.
Patients taking AMILORETIC should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. AMILORETIC 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 also section 4.3).

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.

Porphyria
The safe use of hydrochlorothiazide is contentious in patients with porphyria.

Excipients
Lactose warning:
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

Sunset yellow FCF Lake (C.I. No. 15895)
May cause allergic reactions.

Paediatric population
AMILORETIC is contraindicated in children under 18 years because safety and efficacy have not been established.

4.5 Interaction with other medicines and other forms of interaction

Lithium

Lithium generally should not be given with thiazide diuretics since the association may lead to toxic blood concentrations of lithium. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the prescribing information for lithium preparations before use of such preparations.

Non-Steroidal Anti-inflammatory Drugs Including Selective Cyclooxygenase-2 (COX-2) Inhibitors

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

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 HCl, may cause hyperkalaemia, particularly in elderly patients. Therefore, when amiloride HCl 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:

a) Alcohol, barbiturates or narcotics

Co-administration may potentiate orthostatic hypotension.

b) Oral and parenteral antidiabetic medicines

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

c) Other antihypertensive medicines

Other antihypertensive medicines may have an additive effect. Therefore, the dosage of these medicines, especially adrenergic-blockers, may need to be reduced when AMILORETIC is added to the regimen. Diuretic therapy 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.

d) 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 gastro-intestinal 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%.

e) Corticosteroids or adrenocorticotropic hormone (ACTH)

Corticosteroids, corticotrophin, carbenoxolone or ACTH may intensify any thiazide-induced electrolyte depletion, particularly hypokalaemia.

f) Pressor amines

Pressor amines such as epinephrine (adrenaline) may show decreased arterial responsiveness when used with AMILORETIC but this reaction is not enough to preclude their therapeutic usefulness.

g) Non-depolarising muscle relaxants

Non-depolarising muscle relaxants such as tubocurarine may possibly interact with AMILORETIC to increase muscle relaxation.

h) Medicine/laboratory tests

Because thiazides may affect calcium metabolism, AMILORETIC may interfere with tests for parathyroid function; serum concentrations of protein-bound iodine may increase without signs of thyroid disturbance.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy, lactation and childhood has not been established.

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, neonatal jaundice, 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.

Chlorothiazide crosses the placenta which may cause neonatal jaundice, thrombocytopenia, and electrolyte imbalances.

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 AMILORIDE during breast feeding is not recommended. If AMILORIDE is used during breastfeeding, doses should be kept as low as possible.

Chlorothiazide is excreted in the breast milk. Treatment with thiazide diuretics can inhibit lactation.

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

AMILORETIC has moderate influence on the ability to drive and use machines.

Since adverse reactions such as weakness, fatigue, dizziness, stupor and vertigo have been reported in patients receiving AMILORETIC, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that AMILORETIC does not adversely affect their ability to do so (see section 4.4 and/or 4.8).

4.8 Undesirable effects

a) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
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 the lymphatic system disorders		Granulocytopenia	Blood dyscrasias, thrombocytopenia, leucopenia, aplastic and haemolytic anaemia, neutropenia, purpura
Immune system disorders			Photosensitivity, skin rashes,
Metabolism and nutrition disorders			Increase in blood-urea-nitrogen, hyperkalaemia, elevated plasma potassium levels (above 5.5 mmol/l), electrolyte imbalance, hyponatraemia, gout, dehydration, symptomatic hyponatraemia, glycosuria, hyperglycaemia, hyperuricaemia

Psychiatric disorders			Minor psychiatric, insomnia, nervousness, mental confusion, depression, sleepiness, Encephalopathy, decreased libido, somnolence, restlessness.
Nervous system disorders			Paraesthesia, dizziness, headache, vertigo, stupor
Eye disorders			Visual changes, yellow vision, transient blurred vision, xanthopsia, choroidal effusion
Ear and labyrinth disorders			Tinnitus, increased intra-ocular pressure
Cardiac disorders			Orthostatic hypotension, heart block, palpitations
Vascular disorders			Necrotising angiitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema, pneumonitis, dyspnoea, cough, respiratory distress
Gastrointestinal disorders			Anorexia, gastric irritation, nausea, vomiting, abdominal pain, diarrhea, constipation, thirst, dry mouth, gastrointestinal bleeding, appetite changes, abdominal fullness, flatulence, hiccups, activation of probable pre-existing peptic ulcer, dyspepsia
Hepato-biliary disorders			Cholestatic jaundice, pancreatitis, abnormal liver function,
Skin and subcutaneous tissue disorders			Skin rash, pruritus, flushing, diaphoresis, alopecia, urticaria, toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders			Muscle cramps, leg ache, joint pain, neck/shoulder ache, pain in extremities
Renal and urinary disorders			Renal dysfunction including renal failure, incontinence, nocturia, dysuria, polyuria, urinary frequency, bladder spasm, interstitial nephritis.
Reproductive system and breast disorders			Impotence
General disorders and administrative site conditions			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.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer has been observed.

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

Or Adcock Ingram Limited:

E-mail: Adcock.aereports@adcock.com

Tel: 011 635 0134

4.9 Overdose

Symptoms

Dehydration, hypochloraemic alkalosis and hypokalaemia or hyperkalaemia (see section 4.4 and 4.8).

Treatment

Treatment is symptomatic and supportive. Therapy should be discontinued and the patient watched closely. Emesis should be induced and/or gastric lavage performed. The most common signs and symptoms of overdosage with amiloride hydrochloride are dehydration and electrolyte imbalance. Blood pressure should be monitored and corrected where necessary. If hyperkalaemia occurs, active measures should be taken to reduce the plasma potassium levels.

Electrolyte depletion (hypokalaemia, hypochloremia, hyponatraemia) and dehydration are the most common signs and symptoms of hydrochlorothiazide overdosage. If digoxin has been administered, hypokalaemia may accentuate cardiac dysrhythmias.

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: C03AX01

Mechanism of action

Hydrochlorothiazide and amiloride are both oral diuretics which act by reducing reabsorption of electrolytes from the renal tubules thereby increasing the excretion of sodium and chloride ions and consequently of water.

Hydrochlorothiazide also increases the excretion of potassium ions while amiloride has the opposite effect and has been found to diminish the kaluretic effects of other diuretics i.e. hydrochlorothiazide in this combination.

Hydrochlorothiazide slightly increases the bicarbonate excretion without appreciable alteration to the acid-base balance of the pH of the urine. It has an anti-hypertensive effect and enhances the action of other hypotensive medicines.

Due to its amiloride component, the urinary excretion of magnesium is less with AMILORETIC than with a thiazide or loop diuretic used alone. The onset of the diuretic action of AMILORETIC is within 2 hours, and this action may still be evident for approximately 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Amiloretic:

Lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, sodium starch glycollate, Sunset Yellow FCF Lake (C.I. No. 15895), purified talc.

Amiloretic H.S.:

Lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, sodium starch glycollate, dye Lennon Lake Yellow (C.I No. 15985), purified talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep in the original packaging until required for use.

6.5 Nature and contents of container

AMILORETIC: 30 or 100 tablets are packed in clear polyvinylchloride blister strips with an aluminium backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

1 000 tablets are packed in a white polypropylene container with a white linear low density polyethylene cap together with a white foam insert and a leaflet.

The tablets are also packed in a metallised lay flat bag sealed with a zip-lock for lay-flat.

AMILORETIC H.S.TABLETS: 30 or 100 tablets are packed in clear polyvinylchloride blister

strips with an aluminium backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

1 000 tablets are packed in a white polypropylene container with a white linear low density polyethylene cap together with a white foam insert and a leaflet.

The tablets are also packed in a metallised lay flat bag sealed with a zip-lock for lay-flat.

Not all packs and pack size are necessarily 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

AMILORETIC: L/18.1/396
AMILORETIC H.S.TABLETS:U/18.1/40

9. DATE OF FIRST AUTHORISATION

AMILORETIC: 23 September 1979
AMILORETIC H.S. TABLETS: 06 August 1987

10. DATE OF REVISION OF TEXT

19 JUNE 2023

Namibia		
NS2	Amiloretic H.S. Tablets	90/18.1/00786
NS2	Amiloretic	90/18.1/00787
Botswana		
S2	Amiloretic H.S. Tablets	B9322045
S2	Amiloretic	B9322040