

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMORIDE/Amiloride 5 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amiloride hydrochloride BP equivalent to 5mg anhydrous amiloride hydrochloride.

Excipient with known effect:

Also contains 75.0mg lactose per tablet. For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

Flat cream coloured tablets, odourless engraved Amoride on one side and scored on the other

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

While Amiloride may be used independently, its main indication is for concurrent therapy with either thiazide diuretics such as hydrochlorothiazide or loop diuretics such as furosemide in order to conserve potassium in those at risk from hypokalaemia during episodes of vigorous diuresis and during long-term maintenance therapy.

Amiloride is indicated in the treatment of:

- (i) Congestive heart failure
- (ii) Hypertension, as an adjunctive agent
- (iii) Oedema associated with hepatic cirrhosis (including ascites).

4.2. Posology and Method of Administration

Posology:

Adults:

The initial dosage should be 10 mg either as a single dose or 5 mg twice a day. This may be increased if necessary, but must not exceed 20 mg (4 tablets) per day. After diuresis has been achieved, the dosage may be reduced to the least amount required (by 5 mg increments).

Amiloride with other diuretic therapy

Congestive heart failure:

Amiloride may be started at a dosage of 2.5 mg (½ tablet) a day, together with the usual dosage of other diuretic agents. If diuresis is not achieved with minimal dosage of both agents, the dosage of both may be gradually increased, but that of Amiloride should not exceed 10 mg (2 tablets) a day. Once diuresis has been achieved, reduction in dosage of both agents may be attempted for maintenance therapy. The dosage of both agents should be determined by the diuretic response and the plasma potassium level.

Hypertension

Amiloride is given at a dosage of 2.5 mg to 10 mg (½ to 2 tablets) a day, together with the usual antihypertensive dosage of thiazides.

Hepatic cirrhosis with ascites

Treatment should be started with a small dose of Amiloride, i.e. 5 mg (1 tablet), plus a low dosage of the other diuretic agent. If necessary, dosage of both agents may be increased gradually until there is effective diuresis.

The dosage of Amiloride should not exceed 10 mg (2 tablets) a day. Maintenance doses may be lower than those required to initiate diuresis; reduction in the daily dosage should therefore be attempted when the patient's weight is stabilised. Gradual weight reduction in cirrhotic patients is especially desirable to reduce the likelihood of untoward reactions.

Older People:

Because the elderly are more susceptible to electrolyte imbalance and because renal reserve may be reduced, they are more likely to experience hyperkalaemia. The dosage should be adjusted according to renal function, blood electrolytes and diuretic response.

Paediatric Population:

The use of Amiloride is not recommended in children.

Method of Administration: Oral

4.3. Contra-indications

Hypersensitivity to amiloride or to any of the excipients listed in section 6.1

Hyperkalaemia (plasma potassium over 5.5 mmol/l), other potassium conserving agent or potassium supplements (see section 4.4)

Anuria,

Acute renal failure, severe renal impairment, diabetic nephropathy (see section 4.4)

Addison's disease

4.4. Special Warnings and Precautions for Use

Diabetes Mellitus:

To minimise the risk of hyperkalaemia in known or suspected diabetic patients, the status of renal function should be determined before initiating therapy. Amiloride should be discontinued at least three days before a glucose tolerance test because of the risks of provoking severe hyperkalaemia.

Metabolic or respiratory acidosis:

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 of decompensated diabetes. 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.

Hyperkalaemia:

This has been observed in patients receiving Amiloride, alone or with other diuretics. These patients should be observed carefully for clinical, laboratory and ECG evidence of hyperkalaemia.

Some deaths have been reported in this group of patients. Hyperkalaemia has been noted particularly in the elderly and in hospital patients with hepatic cirrhosis or cardiac oedema who

have known renal involvement who were seriously ill, or were undergoing vigorous diuretic therapy. Neither potassium-conserving agents nor a diet rich in potassium should be used with Amiloride except in severe and/or refractory cases of hypokalaemia. If the combination is used, plasma potassium levels must be continuously monitored, (see section 4.3).

It is also important to bear in mind that administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can cause severe hyperkalaemia, (see section 4.5).

Impaired renal function:

Patients with increases in blood urea over 10 mmol/l, serum creatinine over 130 umol/l, or with diabetes mellitus, should not receive Amiloride without careful frequent monitoring of serum electrolytes and blood urea levels. In renal impairment, use of a potassium-conserving agent may result in rapid development of hyperkalaemia, (see section 4.3).

Electrolyte imbalance and blood urea increases:

Hyponatraemia and hypochloraemia may occur when Amiloride is used with other diuretics. Reversible increases in blood urea levels have been reported accompanying vigorous diuresis, especially when diuretics were used in seriously ill patients, such as those with hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant oedema. Careful monitoring of serum electrolytes and blood urea levels should therefore be carried out when Amiloride is given with oral diuretics to such patients.

Hepatic impairment:

Oral diuretic therapy is more frequently accompanied by side effects in patients with hepatic cirrhosis with or without ascites, because these patients are intolerant of acute shifts in electrolyte balance, and because they often already have hypokalaemia as a result of associated aldosteronism, (see section 5.2).

Hepatic encephalopathy has been reported in patients with pre-existing severe liver disease.

Excipient warnings:

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose/galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of Interaction

Antimania

Lithium should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity.

Drugs to treat diabetes:

When combined with thiazide diuretics Amiloride can act synergistically with chlorpropamide to increase the risk of hyponatraemia. Canagliflozin might increase the risk of hypotension. Hypotensive and hyperglycaemic effects may be enhanced when diuretics are given with diazoxide.

Anti-epileptics:

There is an increased risk of hyponatraemia when diuretics are given with carbamazepine.

Immunosuppressants:

There is an increased risk of hyperkalaemia with ciclosporin and tacrolimus. Concomitant use with platinum compounds may increase the risk of nephrotoxicity and ototoxicity. Aldesleukin may produce an enhanced hypotensive effect when given with diuretics.

Analgesics:

There is a risk of decreased renal function and the development of hyperkalaemia with NSAIDs (e.g. indometacin). The effects of diuretics are antagonised by ketorolac.

Anti-hypertensives:

The risk of hyperkalaemia may be increased when amiloride is administered concomitantly with ACE inhibitors or angio-tensin-II-converting enzyme inhibitors. Accordingly, when concomitant use of these agents is indicated, because of demonstrated hypokalaemia, frequent monitoring of serum potassium should be instituted and caution should be exercised with the use of these agents. There is an increased risk of hyperkalaemia when potassium-sparing diuretics are given with aliskiren.

Concurrent administration of ACE inhibitors, adrenergic neurone blockers, alpha blockers, angiotensin-II receptor antagonists, beta blockers, calcium channel blockers, clonidine, hydralazine, methyl dopa, minoxidil, moxisylyte, moxonidine, nitrates, sodium nitroprusside, may enhance the hypotensive effect.

Anti-depressants:

There is an increased risk of postural hypotension when diuretics are given with tricyclic antidepressants and MAOIs.

Corticosteroids:

Corticosteroids antagonise the diuretic effect of diuretics.

Antibiotics:

Amiloride can cause a small reduction in the absorption of amoxicillin. Lymecycline should be avoided because of its association with rises in blood urea nitrogen levels. The nephrotoxic effects of tetracyclines may be exacerbated by diuretics. Trimethoprim may cause hyperkalaemia and this may be additive with the effects of potassium-sparing diuretics.

Anti-protozoals:

Pentamidine is structurally similar to amiloride and therefore use with potassium-sparing diuretics may result in severe hyperkalaemia.

Ulcer-healing agents:

Amiloride can oppose the ulcer healing effect of carbenoxolone.

Cardiac glycoside (Digoxin):

Amiloride has little effect on digoxin levels in healthy subjects, but it might reduce its inotropic effects, and in patients with renal impairment amiloride possibly raises digoxin levels.

Alcohol:

Alcohol may enhance the hypotensive effect of diuretics.

Prostaglandins:

There is an enhanced hypotensive effect when diuretics are given with alprostadil.

General anaesthetics

There is an enhanced hypotensive effect when diuretics are given with general anaesthetics.

Anxiolytics and Hypnotics:

There is an enhanced hypotensive effect when diuretics are given with anxiolytics and hypnotics.

Muscle relaxants:

There is an enhanced hypotensive effect when diuretics are given with baclofen or tizanidine.

Anti-Parkinsonism drugs:

There is an enhanced hypotensive effect when diuretics are given with levodopa, co-beneldopa or co-careldopa.

Anti-psychotics:

There is an enhanced hypotensive effect when diuretics are given with phenothiazines.

Hormones:

The diuretic effect of diuretics is antagonised by oestrogens. There is a risk of hyperkalaemia when potassium-sparing diuretics are given with drospirenone and the hormone antagonist trilostane.

Total Parenteral Nutrition:

There are reports of patients receiving total parenteral nutrition (TPN) are developing metabolic acidosis associated with concurrent use of amiloride; it is suggested that the reason for this is because the diuretics prevented the kidneys from responding normally to the acid load from the TPN. Caution is advised during the concurrent use.

Potassium Supplements:

There is an increased risk of hyperkalaemia when amiloride is given with potassium supplements or with other potassium-sparing diuretics.

4.6. Fertility, Pregnancy and Lactation

Pregnancy:

Amiloride is not recommended for use during pregnancy. The potential benefits of the drug must be weighed against possible hazards to a foetus if it is administered to women of childbearing age.

It has been found that the routine use of diuretics in otherwise healthy pregnancy women with or without mild oedema is not indicated because they may be associated with hypovolaemia, increased blood viscosity and decreased placental perfusion. Foetal and neonatal jaundice, foetal bone depression and thrombocytopenia have also been described.

Breast-feeding: It is not known whether Amiloride is excreted in human milk. Because of the potential for serious adverse reactions in the nursing infant a decision should be made whether the mother should stop nursing or whether mothers should stop taking the drug.

4.7 Effects on ability to drive and use machines

None stated

4.8. Undesirable Effects

Blood and lymphatic system disorders:

Rise in blood urea-nitrogen concentrations, (*aplastic anaemia, *neutropenia)

Metabolism and nutrition disorders:

Anorexia, hyperkalaemia (plasma potassium levels over 5.5 mmol/l), hyponatraemia (when used with other diuretics), metabolic acidosis

Psychiatric disorders:

Nervousness, agitation, mental confusion, insomnia, somnolence, decreased libido, depression, minor psychiatric changes

Nervous system disorders:

Headache, dizziness, paraesthesia, tremor, encephalopathy

Eye disorders:

Minor visual disturbances, increased intra-ocular pressure

Ear and labyrinth disorders:

Tinnitus, vertigo

Cardiac disorders:

Angina pectoris, arrhythmias, palpitation

One patient with a partial heart block developed complete heart block.

Vascular disorders:

Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:

Cough, nasal congestion, dyspnoea

Gastrointestinal disorders:

Nausea, vomiting, diarrhoea, constipation, abdominal pain, thirst, dyspepsia, heartburn, flatulence, dry mouth, GI bleeding, (*activation of likely pre-existing peptic ulcer)

Hepatobiliary disorders:

Jaundice (*abnormal liver function tests)

Skin and sub-cutaneous disorders:

Mild Skin rashes, pruritus, alopecia

Musculoskeletal and connective tissue disorders:

Muscle cramps, joint pain, back pain, chest pain, neck/shoulder ache, pain in extremities

Renal and urinary disorders:

Urinary disturbances: polyuria, dysuria, bladder spasms, urinary frequency

Reproductive system and breast disorders:

Sexual dysfunction, impotence

General disorders and administration site conditions:

Weakness, fatigue, malaise

*Unknown causal relationship

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It

allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme [www.mhra.gov.uk/yellowcard].

4.9 Overdose

It is not known whether the drug is dialysable. Dehydration and electrolyte imbalance should be treated by established procedures. Amiloride should be stopped and the patient observed closely. No specific antidote is available. Gastric lavage should be performed if of recent ingestion. Treatment is symptomatic and supportive. Plasma potassium levels should be reduced if hyperkalaemia occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Other Potassium sparing agents,

ATC code: C03DB01

Amiloride takes effect about two hours after administration by mouth and its diuretic action persists for about 24 hours. It acts mainly on the distal renal tubules. It increases the excretion of sodium and chloride and reduces the excretion of potassium.

Amiloride enhances the natriuretic and diminishes the kaliuretic effects of other diuretics.

5.2. Pharmacokinetic Particulars

Amiloride is in-completely absorbed from the gastro-intestinal tract; bioavailability is about 50% and is reduced by food. It is not significantly bound to plasma proteins and has a plasma half-life of 6 to 9 hours; the terminal half-life may be 20 hours or more. It is excreted unchanged in the urine.

Peak serum concentrations are reached in about four hours after a dose.

Hepatic impairment:

In patients with acute hepatitis the terminal half-life of amiloride was 33 hours compared with 21 hours in healthy subjects. The proportion of the dose excreted in the urine was increased from 49 to 80%

Renal impairment:

Studies of the pharmacokinetics of amiloride have reported an increase in terminal elimination half-life from 20 hours in healthy subjects to 100 hours in patients with end-stage renal disease. The natriuretic effect of amiloride was reduced in patients with creatinine clearance below 50 mL/minute. In patients with renal impairment amiloride could aggravate potassium retention due to renal disease. Studies in elderly patients have found increased half-life and steady state concentrations associated with reduced renal function.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose
Calcium hydrogen phosphate
Pregelatinised maize starch
Maize starch
Magnesium stearate

6.2. Incompatibilities

None stated

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C in a dry place in well closed containers.
Protect from light.

6.5 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane/polythene inserts.
Pack sizes: 28, 30, 50, 56, 60, 100, 250, 500 & 1000

Blister pack:

20 micron hard-tempered aluminium foil, coated on the dull side with 6-7 gsm heat-seal lacquer and printed on the bright side; 250 micron rigid, green PVC Pharmaceutical Grade.

Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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3rd floor, 1060 Nicosia

Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0004

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24.06.1996

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19/10/2015