

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amiloride 5mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amiloride Hydrochloride BP 5.675mg equivalent to anhydrous Amiloride Hydrochloride 5mg

Excipient(s) with known effect:

Liquid maltitol (E965) 3415mg/5ml

Methyl hydroxybenzoate (E218) 6mg/5ml

Propyl hydroxybenzoate (E216) 1.5mg/5ml

Propylene glycol (E1520) 103.5mg/5ml

Ethanol 3.7mg/5ml

For excipients see section 6.1

3 PHARMACEUTICAL FORM

Solution for oral administration

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Potassium - conserving agent; diuretic.

Although Amiloride Hydrochloride may be used alone, its principal indication is as concurrent therapy with thiazides or more potent diuretics to conserve potassium during periods of vigorous diuresis and during long term maintenance therapy.

In hypertension, it is used as an adjunct to prolonged therapy with thiazides and similar agents to prevent potassium depletion.

In congestive heart failure, Amiloride Hydrochloride may be effective alone, but its principal indication is for concomitant use in patients receiving thiazides or more potent diuretic agents.

In hepatic cirrhosis with ascites, Amiloride Hydrochloride usually provides adequate diuresis, with diminished potassium loss and less risk of metabolic alkalosis, when used alone. It may be used with more potent diuretics when a greater diuresis is required while maintaining a more balanced serum electrolyte pattern.

4.2 Posology and method of administration

Adults:

Amiloride Hydrochloride alone. The usual initial dosage is 10mg (as a single dose or 5mg twice a day). The total daily dose should not exceed 20mg (20ml) a day. After diuresis has been achieved, the dosage may be reduced by 5mg (5ml) increments to the least amount required.

Amiloride Hydrochloride with other diuretic therapy

When Amiloride is used with a diuretic which is given on an intermittent basis, it should be given at the same time as the diuretic.

Hypertension

Usually 2.5mg (2.5ml) given once a day together with the usual antihypertensive dosage of the thiazide concurrently employed. If necessary, increase to 5mg (5ml) given once a day or in divided doses.

Congestive heart failure

Initially 2.5mg (2.5ml) a day together with the usual dose of the diuretic concurrently employed, subsequently adjusted if required, but not exceeding 10mg (10ml) a day. Optimal dosage is determined by the diuretic response and the plasma potassium level. Once an initial diuresis has been achieved, reduction in dosage may be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

Hepatic Cirrhosis with ascites

Initiate therapy with a low dose. A single daily dose of 5mg (5ml) plus a low dosage of the other diuretic agent may be increased gradually until there is an effective diuresis. The dosage of Amiloride Hydrochloride should not exceed 10mg (10ml) a day. Maintenance dosages may be lower than those required to initiate diuresis; dosage reduction should therefore be attempted when the patient's weight is stabilised. A gradual weight reduction is especially desirable in cirrhotic patients to reduce the likelihood of untoward reactions associated with diuretic therapy.

Children

The use of Amiloride Hydrochloride in children under 18 years of age is not recommended as safety and efficacy have not been established.

Elderly

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

4.3 Contraindications

Hyperkalaemia (plasma potassium over 5.5mmol/l) other potassium-conserving agents or potassium supplements (see Precautions); Addison's disease; anuria; acute renal failure, severe progressive renal disease, diabetic nephropathy (see Precautions); prior sensitivity to this product. Safety for use in children is not established. See also 'Use in Pregnancy' and 'Use in the Breast Feeding mother'.

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 Hydrochloride should be discontinued for at least three days before a glucose-tolerance test.

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 or 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 Hydrochloride, alone or with other diuretics. These patients should be observed carefully for clinical, laboratory or 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 Hydrochloride except in severe and/or refractory cases of hypokalaemia. If the combination is used, plasma potassium levels must be continuously monitored.

Impaired Renal Function

Patients with increases in blood urea over 10mmol/l, serum creatinine over 130µmol/l, or with diabetes mellitus, should not receive Amiloride Hydrochloride 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.

Treatment of Hyperkalemia

If hyperkalaemia occurs, Amiloride Hydrochloride should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level.

Electrolyte Imbalance and Reversible Blood Urea Increases.

Hyponatraemia and hypochloraemia may occur when Amiloride Hydrochloride 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 Hydrochloride is given with other diuretics to such patients.

Cirrhotic patients

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.

In patients with pre-existing severe liver disease, hepatic encephalopathy manifested by tremors, confusion and coma, and increased jaundice has been reported in association with diuretics, including Amiloride Hydrochloride.

Excipient Warnings

This product contains:

- Liquid maltitol (E965). Patients with rare hereditary problems of fructose should not take this medicine.
- Methyl and propyl hydroxybenzoates are contained in this product which may cause allergic reactions (possibly delayed).
- Propylene glycol (E1520) 103.5mg in each 5ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.
- Ethanol. This medicine contains 3.7 mg of alcohol (ethanol) in each 5 ml. The amount in 5 ml of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

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

When combined with thiazide diuretics, amiloride can act synergistically with chlorpropamide to increase the risk of hyponatraemia.

Hyponatraemia and hypochloraemia may occur when Amiloride is used with other diuretics (See Section 4.4 Special warnings and precautions for use).

When Amiloride Hydrochloride is administered concomitantly with an angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, trilostrane, ciclosporin or tacrolimus, the risk of hyperkalaemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

The concomitant administration of Amiloride and NSAIDs may lead to an increased risk of nephrotoxicity, an antagonism of the diuretic effect and possibly an increased risk of hyperkalaemia, particularly in elderly patients. Therefore, when amiloride hydrochloride is used concomitantly with NSAIDs, renal function and serum potassium levels should be carefully monitored.

4.6 Fertility, Pregnancy and lactation

Because clinical experience is limited, Amiloride Hydrochloride is not recommended for use during pregnancy. 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.

Foetal and neonatal jaundice, foetal bone marrow depression and thrombocytopenia have also been described. The potential benefits of the drug must be weighed against the possible hazards to the foetus if it is administered to a woman of child bearing age.

It is not known whether Amiloride Hydrochloride is excreted in human milk. Because many drugs are excreted by this route, and because there is a risk that it might take this route of excretion and that it might then cause serious side effects in the breast feeding infant, the mother should either stop breast feeding or stop taking the drug. The decision depends on the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Amiloride Hydrochloride is normally well tolerated, although minor side effects are reported relatively frequently. Except for hyperkalaemia, significant side effects are infrequent. Nausea, anorexia, abdominal pain, flatulence and mild skin rash are probably due to Amiloride; but other side effects are generally associated with diuresis or with the underlying condition being treated.

Body as a whole

Headache, weakness, fatigue, back pain, chest pain, neck/shoulder ache, pain in the extremities.

Cardiovascular

Angina pectoris, orthostatic hypotension, arrhythmias, palpitation, one patient with partial heart block developed complete heartblock.

Digestive

Anorexia, nausea, vomiting, diarrhoea, constipation, abdominal pain, GI bleeding, jaundice, thirst, dyspepsia, flatulence.

Metabolism and nutrition disorders

Elevated plasma potassium levels above 5.5mmol/l, hyponatraemia. Serum uric acid levels may rise during treatment with Amiloride and acute attacks of gout may be precipitated.

Integumentary

Pruritus, rash, dryness of mouth, alopecia.

Musculoskeletal

Muscle cramps, joint pain. Serum uric acid levels may rise during treatment with Amiloride and acute attacks of gout may be precipitated.

Nervous

Dizziness, vertigo, paraesthesiae, tremors, encephalopathy.

Psychiatric

Nervousness, mental confusion, insomnia, decreased libido, depression, somnolence.

Respiratory

Cough, dyspnoea.

Special Senses

Nasal congestion, visual disturbances, increased intra-ocular pressure, tinnitus.

Urogenital

Impotence, polyuria, dysuria, bladder spasm, frequency of micturition.

Reactions in which no causal relationship could be established were activation of probable pre-existing peptic ulcer, aplastic anaemia, neutropenia and abnormal liver function tests. In a few cirrhotic patients, jaundice associated with the underlying disease had deepened but the drug relationship is uncertain.

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

No data are available; and it is not known whether the drug is dialysable.

The most likely signs and symptoms are dehydration and electrolyte imbalance which should be treated by established methods. Therapy should be discontinued and the patient observed closely. No specific antidote is available. If ingestion is recent, emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive. If hyperkalaemia occurs, active measures should be taken to reduce plasma potassium levels.

The plasma half life of amiloride is about six hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Amiloride has mild diuretic and anti-hypertensive activity. It acts primarily in the distal tubule and does not require aldosterone for its action. Amiloride is a mild natriuretic which does not initiate a concomitant decrease in potassium levels. The mechanism of action includes inhibition of the electrogenic entry of sodium thus causing a fall in the electrical potential across the tubular epithelium. Since this potential is one of the main causes of the secretion of potassium, this mechanism is likely to be the basis of the potassium sparing effect. By blocking the sodium channels, Amiloride may also reduce exchange of Na⁺ ions and H⁺ ions. A combination of the Amiloride with a benzothiadiazine diuretic will cause less magnesium excretion than the diuretic alone.

5.2 Pharmacokinetic properties

Amiloride is incompletely absorbed from the gastro-intestinal tract, only about 50% is recovered unchanged in the urine following an oral dose. The drug is not metabolised and can, therefore, be useful in patients with liver disease. Peak plasma concentrations are reached about 3 - 4 hours after oral administration and the plasma half-life is in the range of 6 - 9 hours.

In a 70Kg man, the distribution volume is about 5L/Kg, suggesting that the drug is widely distributed in the tissues. Amiloride appears to be weakly bound to plasma proteins as determined by electrophoretic and gel filtration studies. It is not known whether the drug is excreted in breast milk, although studies have shown the presence of Amiloride in the breast milk of rats.

Amiloride is excreted unchanged in the urine. In two studies in which single doses of ¹⁴C-Amiloride were used, approximately 50% was recovered in urine and 40% in the faeces within 72 hours. In radioactive studies, peak plasma levels of 38 - 40µg/L were seen three to four hours after a single 20mg oral dose. These low plasma levels are thought to be due to extravascular distribution as evidenced by the large volume of distribution.

In man, the calculate renal clearance of Amiloride exceed in the glomerular filtration, suggesting that there is a tubular secretory pathway. Renal clearance of the drug does not appear to be affected by probenecid, pH of the urine or urinary flow rate.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid Monohydrate Ph Eur

Methyl Hydroxybenzoate (E218) Ph Eur

Propyl Hydroxybenzoate (E216) Ph Eur

Propylene Glycol (E1520) Ph Eur

Vanillin Ph Eur

Compound Orange Spirit BP (contains ethanol)

Liquid Maltitol (E965) Ph Eur

Purified Water Ph Eur

6.2 Incompatibilities

None known

6.3 Shelf life

Shelf life in marketed pack 12 months

6.4 Special precautions for storage

Store at or below 25°C, out of reach of children

6.5 Nature and contents of container

Glass (Type III) amber bottle, with capacities of 150ml

Closures: HDPE EPE wadded, tamper evident, child resistant

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

Essential Pharma Limited
8a Crabtree Road, Egham,
Surrey, TW20 8RN,
UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 41871/0017

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21/11/1995 / 17/04/2001

10 DATE OF REVISION OF THE TEXT

19/09/2024