1 NAME OF THE MEDICINE
Amiloride hydrochloride dihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
The active ingredient of Kaluril tablets is amiloride hydrochloride dihydrate. Each Kaluril tablet contains 5 mg of amiloride hydrochloride dihydrate.

Kaluril also contains lactose monohydrate. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM
5 mg tablet: pale yellow, flat bevelled edge, scored on one side, marked AR|5 on one side, G on reverse.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Kaluril's main indication is as concomitant therapy with diuretics to conserve potassium during periods of vigorous diuresis and during long-term maintenance therapy with thiazides or other more potent diuretics. Kaluril when used alone, has mild diuretic and antihypertensive activity.

**Oedema of cardiac origin.** Although Kaluril alone may provide adequate diuresis for some patients with oedema of cardiac origin, it is primarily indicated for concomitant use in patients receiving thiazides or more potent saluretic-diuretic agents. In these patients it may provide increased sodium, chloride and water excretion and decreased potassium excretion. The positive effect of Kaluril on potassium balance may be especially important for digitalised cardiac patients, in whom potassium depletion sensitises or exaggerates the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability), which may precipitate digitalis intoxication with potentially serious cardiac arrhythmias.

**Hypertension.** Kaluril is used as an adjunctive agent for the prevention of potassium depletion in patients receiving thiazides or other oral saluretic antihypertensive therapy over a prolonged period. When combined with hydrochlorothiazide, Kaluril produces an additive antihypertensive effect.

**Hepatic cirrhosis with ascites and oedema.** Kaluril, when used alone, usually provides adequate diuresis with diminished potassium loss and with a reduced risk of metabolic alkalosis. Kaluril may also be used with other more potent saluretic diuretic agents where greater diuresis is needed while maintaining a more balanced serum electrolyte pattern.

As with all therapy for the ascites of hepatic cirrhosis, gradual weight loss and avoidance of electrolyte imbalance are the chief objectives (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.2 DOSE AND METHOD OF ADMINISTRATION
**General considerations.** Kaluril usually begins to act within 2 hours following oral administration. Its effect upon electrolyte excretion reaches a peak between 6 and 10 hours and lasts for approximately 24 hours. Most patients respond during the first day of treatment; however, maximum therapeutic effect may not be seen for several days.

The rate of weight loss and serum electrolyte levels should determine the dose. After initiating diuresis, the most satisfactory rate of weight loss is generally about 0.5 to 1.0 kg daily.
**Kaluril alone.** The initial dosage should be 10 mg (as a single dose or 5 mg twice daily). Dosage may be increased, depending upon the need for effective potassium sparing action, but must not exceed 20 mg daily. Once diuresis has been achieved, the dosage may be reduced by 5 mg increments to the least amount required.

**Kaluril plus other diuretic therapy.** Oedema of cardiac origin. Kaluril, 5 or 10 mg daily, may be employed with the usual doses of other saluretic diuretic agents. If diuresis is not achieved with minimal doses of both agents, the dosage of both drugs may be gradually increased. The dosage of Kaluril should not exceed 20 mg/day. Once diuresis is achieved, reduction in dosage of both agents may be attempted. The dosage of both drugs is determined by the diuretic response and the serum potassium level.

**Hypertension.** 5 or 10 mg daily, given with the usual antihypertensive doses of thiazides. The dosage may be adjusted if necessary. It is not usually necessary to exceed 10 mg of Kaluril daily; in any event, no more than 20 mg daily should be administered.

**Hepatic cirrhosis with ascites.** Treatment should be initiated with a small dose of Kaluril, i.e. 5 mg, plus low doses of any other saluretic diuretic agent that may be employed. If necessary, dosages of both drugs may be increased gradually until there is effective diuresis. The dosage of Kaluril should not exceed 20 mg daily. Maintenance doses may be lower than those required to initiate diuresis; therefore, reduction in the daily dose should 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.

### 4.3 CONTRAINDICATIONS

**Hyperkalaemia.** Amiloride hydrochloride dihydrate should not be used in the presence of elevated serum potassium levels (interpreted as over 5.5 mmol/L).

**Antikaliuretic therapy or potassium supplementation.** Kaluril should not be given to patients receiving other potassium conserving agents, such as spironolactone or triamterene. Potassium supplementation in the form of medication or a potassium rich diet should not be used with Kaluril except in severe and/or refractory cases of hypokalaemia. Such concomitant therapy can be associated with rapid increases in serum potassium levels. If potassium supplementation is used, careful monitoring of the serum potassium level is necessary.

**Impaired renal function.** Anuria, acute renal failure, severe progressive renal disease, and diabetic nephropathy are contraindications to use of amiloride hydrochloride dihydrate. Patients with increases in BUN over 30 mg/100 mL (10.7 mmol/L), in serum creatinine levels over 1.5 mg/100 mL (0.13 mmol/L), or in whole blood urea values over 60 mg/100 mL (10 mmol/L), should not receive the drug 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 agent and may result in the rapid development of hyperkalaemia.

**Known sensitivity to the drug.** As with all drugs, prior sensitisation is a contraindication to the use of the compound.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Diabetes mellitus**

In diabetic patients, hyperkalaemia has commonly occurred during therapy with amiloride hydrochloride dihydrate, particularly if chronic renal disease or prerenal azotaemia is present. The status of renal function should therefore be known before starting therapy in diabetic or suspected diabetic patients.

One patient with poorly controlled diabetes mellitus, who became severely hyperkalaemic while on amiloride hydrochloride dihydrate, died following 2 repeated intravenous glucose tolerance tests. Therefore, therapy should be discontinued for at least 3 days in any suspected diabetic patient on Kaluril who requires glucose tolerance testing.

**Metabolic or respiratory acidosis**

In severely ill patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease and patients with decompensated diabetes, antikaliuretic therapy should be instituted.
only with caution. Shifts in acid-base balance alter the balance of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

**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.

Hepatic encephalopathy, manifested by tremors, confusion and coma, has been reported.

In cirrhotic patients, jaundice associated with the underlying disease process has deepened in a few instances but the relationship to the drug is uncertain.

**Hyperkalaemia**

Hyperkalaemia, defined as serum potassium levels over 5.5 mmol/L, has been observed in patients who received amiloride hydrochloride dihydrate, either alone or in combination with other diuretic drugs. This has been noted particularly in aged patients and in hospitalised patients with hepatic cirrhosis or cardiac oedema who have known renal involvement, are seriously ill, or are undergoing vigorous diuretic therapy. These patients should be monitored carefully for clinical, laboratory and electrocardiographic evidence of hyperkalaemia. Some deaths have been reported in this group of patients.

Paraesthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock and serum potassium and ECG abnormalities are warning signs of hyperkalaemia. As hyperkalaemia is not always associated with an abnormal electrocardiogram, careful monitoring of the serum potassium level is important. When abnormal, the ECG in hyperkalaemia is characterised primarily by tall, peaked T waves or elevations from previous tracings. There may also be lowering of the R wave and increased depth of the S wave, widening and even disappearance of the P wave, progressive widening of the QRS complex, and prolongation of the PR interval and ST depression.

In the event of hyperkalaemia occurring in patients taking Kaluril, the drug should be discontinued immediately and, if necessary, active measures taken to reduce the plasma potassium level. Discontinuation of antikaliuretic therapy should be followed by intravenous administration of molar sodium lactate or oral or parenteral glucose with a rapid acting insulin. If needed, a cation exchange resin such as sodium polystyrene sulfonate may be given orally or by enema. Patients with persistent hyperkalaemia may require dialysis.

**Electrolyte imbalance and reversible BUN increases**

Hyponatraemia and hypochloraemia may occur when amiloride hydrochloride dihydrate is used with other diuretics and increases in BUN levels have been reported. These increases usually have accompanied vigorous fluid elimination, especially when diuretic therapy was used in seriously ill patients, such as those who had hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant oedema. Therefore, careful monitoring of serum electrolytes and BUN levels is important when Kaluril is given with other diuretics to such patients. In patients with pre-existing severe liver disease, hepatic encephalopathy, manifested by tremors, confusion, and coma, and increased jaundice, have been reported in association with diuretics, including amiloride hydrochloride dihydrate.

**Use in the Elderly**

No data available.

**Paediatric Use**

Kaluril is not recommended in the paediatric age group as the safety for use of amiloride hydrochloride dihydrate in children has not been established.

**Effects on Laboratory Tests**

No data available.
4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

When amiloride hydrochloride dihydrate is administered concomitantly with an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, 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.

Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride hydrochloride dihydrate, may cause hyperkalaemia and renal failure, particularly in elderly patients. Therefore, when amiloride hydrochloride dihydrate is concomitantly used with NSAIDs, renal function and serum potassium levels should be carefully monitored.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Reproduction studies in rats at four times the expected maximum daily dose for humans based on body surface area, showed no evidence of impaired fertility.

Use in Pregnancy (Category: C)

Passive transfer of potassium sparing diuretics across the human placenta has been demonstrated. Maternal treatment during pregnancy may result in electrolyte disturbances in the foetus. Teratogenicity studies with amiloride hydrochloride dihydrate in rabbits and mice given doses of 8 and 10 mg/kg respectively (six and three times the maximum human dose, based on body surface area), revealed no evidence of harm to the foetus. At approximately three or more times the expected maximum daily dose for humans, based on body surface area, some toxicity was seen in adult rats and rabbits and a decrease in rat pup growth and survival occurred.

There are, however, no adequate and well controlled studies in pregnant women.

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

Use in Lactation

Studies in rats have shown that amiloride is excreted in milk in concentrations higher than that found in blood. It is not known whether Kaluril is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from amiloride hydrochloride dihydrate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to assess the direct effect of KALURIL on the ability to drive and use machines. However, adverse effects of KALURIL include dizziness and mental confusion which could affect the ability to drive or use machines. See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Kaluril is usually well tolerated and, except for hyperkalaemia (serum potassium levels greater than 5.5 mmol/L, see Precautions), significant adverse effects have been reported infrequently. Minor adverse reactions were reported relatively frequently (about 20%) but the relationship of many of the reports to amiloride hydrochloride dihydrate is uncertain and the overall frequency was similar in hydrochlorothiazide...
treated groups. Nausea, anorexia, abdominal pain, flatulence and mild skin rash have been reported and probably are related to amiloride. Other adverse experiences that have been reported with amiloride are generally those known to be associated with diuresis, or with the underlying disease being treated.

**Body as a whole.** Headache, weakness, fatiguability, back pain, chest pain, neck/shoulder ache, pain in extremities.

**Cardiovascular.** Angina pectoris, orthostatic hypotension, arrhythmia, palpitation; one patient with a partial heart block developed complete heart block.

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

**Metabolic.** Elevated serum potassium levels (> 5.5 mmol/L); hyponatraemia.

**Integumentary.** Pruritus, rash, dryness of mouth, alopecia.

**Musculoskeletal.** Muscle cramps, joint pain.

**Nervous.** Dizziness, vertigo, paraesthesia, tremors, encephalopathy.

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

**Respiratory.** Cough, dyspnoea.

**Special senses.** Nasal congestion, visual disturbances, increased intraocular pressure, tinnitus.

**Urogenital.** Impotence, polyuria, dysuria, bladder spasms, frequency of micturition.

**Causal relationship unknown.** Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Activation of probably pre-existing peptic ulcer; aplastic anaemia; neutropenia; abnormalities of liver function tests.

**Reporting Suspected Adverse Effects**

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No data are available with regard to overdosage in humans. The oral LD$_{50}$ of amiloride hydrochloride dihydrate (calculated as the base) is 56 mg/kg in mice and 36 to 85 mg/kg in rats, depending on the strain.

**Symptoms**

The most likely signs and symptoms to be expected with overdosage are dehydration and electrolyte imbalance. These can be treated by established procedures.

**Treatment**

Therapy with Kaluril should be discontinued and the patient observed closely. There is no specific antidote. Emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive. If hyperkalaemia occurs, active measures should be taken to reduce the serum potassium levels.

It is not known whether this drug is dialysable.
For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMAUCOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Kaluril is a potassium conserving (antikaliuretic) drug which possesses mild natriuretic, diuretic, and antihypertensive activity (compared with thiazide diuretics). These actions may be additive to the effects of thiazides or other saluretic antihypertensive agents. Amiloride hydrochloride dihydrate has potassium conserving activity in patients receiving kaliuretic diuretic agents; its principal use is to conserve potassium in patients receiving diuretic agents in whom excessive potassium losses occur or are expected.

Kaluril interferes with the mechanism involved in the exchange of sodium for potassium in the distal convoluted tubule of the nephron. An increase in sodium and a decrease in potassium and hydrogen ion excretion are induced in the presence or absence of aldosterone, thereby suggesting a direct tubular action of the drug. Sodium excretion increases moderately, while chloride excretion may remain unchanged or increase slowly with continued therapy. This effect may diminish the risk of hypochloroaemic alkalosis encountered with some saluretic agents. The positive effect of Kaluril on potassium balance is usually beneficial; however, potassium retention to the point of hyperkalaemia may be avoided by keeping the dosage of amiloride hydrochloride dihydrate below 20 mg/day.

Amiloride hydrochloride dihydrate, when administered with hydrochlorothiazide, has been shown to result in less excretion of magnesium than thiazide or loop diuretics used alone.

Amiloride hydrochloride dihydrate is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Kaluril usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Effects on electrolytes increase with single doses of amiloride hydrochloride dihydrate up to approximately 15 mg.

Metabolism and Excretion

Amiloride hydrochloride dihydrate is not metabolised by the liver but is excreted unchanged by the kidneys. About 50% of a 20 mg dose of amiloride hydrochloride dihydrate is excreted in the urine and 40% in the stool within 72 hours. Amiloride hydrochloride dihydrate has little effect on glomerular filtration rate or renal blood flow. Because amiloride hydrochloride dihydrate is not metabolised by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Amiloride hydrochloride dihydrate was devoid of mutagenic activity in Salmonella typhimurium with or without a mammalian liver microsomal activation system (Ames test). The potential to cause chromosomal damage has not been investigated.
Carcinogenicity
There was no evidence of a tumorigenic effect when amiloride hydrochloride dihydrate was administered for 92 weeks to mice at doses up to 10 mg/kg/day (3 times the maximum daily human dose, based on body surface area). Amiloride hydrochloride dihydrate has also been administered for 104 weeks to male and female rats at doses up to 6 and 8 mg/kg/day (3.2 and 4.3 times the maximum daily dose for humans, based on body surface area, respectively) and showed no evidence of carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
The tablets also contain lactose monohydrate, maize starch, microcrystalline cellulose, povidone and magnesium stearate.

6.2 INCOMPATIBILITIES
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
Packed in bottles (HDPE) of 50 Tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES
Chemical Structure
The chemical name for amiloride hydrochloride dihydrate is N-amidino-3,5-diamino-6-chloropyrazine-2-carboxamide hydrochloride dihydrate. Its structural formula is:

![Chemical Structure](image)

Molecular formula: C₆H₉Cl₂N₇O₂H₂O
Molecular weight: 302.12

Amiloride hydrochloride dihydrate is a pale yellow to greenish-yellow powder, odourless or almost odourless.

CAS Number
CAS registry number: 17440-83-4
7 MEDICINE SCHEDULE (POISONS STANDARD)
Schedule 4 (Prescription only medicine)

8 SPONSOR
Alphapharm Pty Limited
Level 1, 30 The Bond
30-34 Hickson Road
Millers Point NSW 2000
www.mylan.com.au

9 DATE OF FIRST APPROVAL
15/07/1998

10 DATE OF REVISION
05/07/2019

Summary Table of Changes

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