BIORAJ PHARMACEUTICALS LIMITED	
BRAND NAME: KISIRETIC	**GENERIC NAME: Amiloride Hydrochloride B.P. 5mg Hydrochlorothiazide B.P. 50mg**
SUMMARY OF PRODUCT CHARACTERISTICS	

1. NAME OF THE MEDICINAL PRODUCT

Kisiretic tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 5mg Amiloride hydrochloride and 50 mg hydrochlorothiazide.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Tablets.
Peach-coloured, four edged tablet with BPL on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kisiretic is indicated in those patients with hypertension or with congestive heart failure who develop hypokalemia when thiazide or other kaliuretic diuretics are used alone or in whom maintenance of normal serum potassium level is considered to be clinically important as in digitalized patients, or patient with significant cardiac arrhythmias. Kisiretic may be used alone or as an adjunct to other antihypertensive drugs such as methyldopa or beta-blockers. If used as adjunct, there may be a need to adjust dosage to avoid excessive fall in blood pressure.

4.2 Posology and method of administration

Posology

Hypertension

Adult: 1-2 tablets daily; up to a maximum, of 4 tablets daily or as directed by the physician. Not recommended for children.

Congestive heart failure

Initially half a 'Kisiretic' tablet a day, subsequently adjusted if required, but not exceeding two 'Kisiretic' tablets 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.

Patients with hepatic cirrhosis with ascites

Initiate therapy with a low dose. A single daily dose of one 'Kisiretic' tablet may be increased gradually until there is an effective diuresis. Dosage should not exceed two 'Kisiretic' tablets 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.

Paediatric population

Kisiretic is contraindicated in children less than 18 years because safety and efficacy have not been established.

Elderly patients

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.

Method of administration

Oral use

4.3 Contraindications

Hyperkalemia:Kisiretic should not be used in the presence of elevated serum potassium levels greater than 5.5mg Eq per liter.

Kisiretic should not be given to patients receiving other potassium-conserving agents such as spironolactone or triamterene.

Kisiretic should not be used with potassium supplementation in the form of medication,potassium-containing salt substitutes or potassium-rich diet except in severe and/or refractory cases of hypokalemia.

Kisiretic is contraindicated in anuria, acute or chronic renal insufficiency and evidence of diabetic nephropathy.

Kisiretic is contraindicated in patients in patients who are hypersensitive to this product or to other sulfonamide derived drugs.

4.4 Special warnings and precautions for use

Kisiretic may cause hyperkalemia. This risk is higher in patients with renal impairment or diabetes mellitus.Since hyperkalemia if uncorrected is fatal, it is essential to monitor serum potassium levels carefully in any patient receiving Kisiretic, particularly when first introduced, at the time of dosage adjustments and during any illness that could affect renal function.

The risk of hyperkalemia may be increased when potassium-conserving agents including Kisiretic are administered concomitantly with an angiotensin-converting enzyme inhibitor.

Warning signs or symptoms of hyperkalemia include paraesthesia, muscular weakness and fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities.

Monitoring of the serum potassium level is essential because mild hyperkalemia is not usually associated with an abnormal ECG.

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

Impaired renal function: Renal function should be monitored because the use of 'Kisiretic' in impaired renal function may result in the rapid development of hyperkalaemia. Thiazide diuretics become ineffective when creatinine levels fall below 30 ml/min.

Electrolyte imbalance: Although the likelihood of electrolyte imbalance is reduced by 'Kisiretic', 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. 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 digitalis (e.g., increased ventricular irritability).
Diuretic-induced hyponatraemia is usually mild and asymptomatic. It may become severe and symptomatic in a few patients who will then require immediate attention and appropriate treatment.
Thiazides 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.
Azotaemia: may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotaemia and oliguria develop during treatment of renal disease, 'Kisiretic' should be discontinued.
Hepatic disease: Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease (see 4.3 'Contraindications'), since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
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 'Kisiretic'. Dosage adjustment of antidiabetic agents, 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 'Kisiretic'. 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.
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 has been reported.

Hydrochlorothiazide

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

Acute Respiratory Toxicity

Very rare severe 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, Kisiretic should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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

Sunset yellow FCF E110: May cause allergic reactions.

Eye disorders:

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs 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 drug 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.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium: generally should not be given with diuretics. 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 Agents 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 drugs, 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 drugs, 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 agents, 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 agents 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 drugs may interact with thiazide diuretics:

Alcohol, barbiturates or narcotics: Co-administration may potentiate orthostatic hypotension.

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

Other antihypertensive drugs may have an additive effect. Therefore, the dosage of these agents, especially adrenergic-blockers, may need to be reduced when 'Kisiretic' is 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.

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%.

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

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

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

Drug/laboratory tests: Because thiazides may affect calcium metabolism, 'Kisiretic' may interfere with tests for parathyroid function.

4.6 Fertility, pregnancy and lactation

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.

Breast-feeding

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 'Kisiretic' during breast feeding is not recommended. If 'Kisiretic' is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

Infrequently, 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

Although minor side effects are relatively common, significant side effects are infrequent. Reported side effects are generally associated with diuresis, thiazide therapy, or with the underlying disease.

No increase in the risk of adverse reactions has been seen over those of the individual components.

Side effects that have been reported with the individual components and may be potential side effects of 'Kisiretic' are listed below:

Amiloride:

Body as a whole: neck/shoulder ache, pain in extremities.
Digestive: abnormal liver function, activation of probable pre-existing peptic ulcer, dyspepsia, jaundice.
Integumentary: dry mouth, alopecia.
Nervous: tremors, encephalopathy.
Haematological: aplastic anaemia, neutropenia.
Cardiovascular: one patient with partial heart block developed complete heart block, palpitation.
Psychiatric: decreased libido, somnolence.
Respiratory: cough.
Special senses: tinnitus, increased intra-ocular pressure.
Urogenital: polyuria, urinary frequency, bladder spasm.

Hydrochlorothiazide:

Body as a whole: fever.
Cardiovascular: necrotising angiitis (vasculitis, cutaneous vasculitis).
Digestive: jaundice (intrahepatic cholestatic jaundice), pancreatitis, cramping, gastric irritation.
Endocrine/Metabolic: glycosuria, hyperglycaemia, hyperuricaemia, hypokalaemia.
Integumentary: photosensitivity, sialadenitis, urticaria, toxic epidermal necrolysis.
Haematological: agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, purpura, thrombocytopenia.
Psychiatric: restlessness.
Renal: interstitial nephritis.
Respiratory: respiratory disorder (including pneumonitis and pulmonary oedema),
Very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4).
Eye disorders: transient blurred vision, xanthopsia, choroidal effusion.
Neoplasms Benign, malignant and unspecified (incl cysts and polyps): Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

4.9 Overdose

No specific data are available on overdosage with 'Kisiretic'. No specific antidote is available, and it is not known whether the drug is dialysable.

Treatment should be 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 digitalis has been administered, hypokalaemia may accentuate cardiac arrhythmias.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretic and potassium-sparing agent

ATC code: C03EA01

Mechanism of action

Kisiretic is an antihypertensive diuretic drug combining the potassium-conserving action of Amiloride HCL with natriuretic action of Hydrochlorothiazide.

Amiloride HCL inhibits sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct, thus decreasing the net negative potential of the tubular lumen. Hence, reducing both potassium and hydrogen secretion and consequently their secretion.

Hydrochlorothiazide is a diuretic antihypertensive drug. It inhibits sodium reabsorption in distal renal tubules, resulting in increased excretion of water, sodium, potassium and hydrogen ions.

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.

5.3 Preclinical safety data

No relevant data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Maize starch
- Lactose powder
- Methyl paraben
- Propyl paraben
- Sunset Yellow
- Allura Red
- Magnesium stearate
- Purified Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from sunlight.

6.5 Nature and contents of container

PVC blister packs, lidded with aluminium foil containing 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.0 MANUFACTURER

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