

NATRILIX SR

COMPOSITION

Active Ingredient : Indapamide hemihydrate 1.5 mg
Excipients : Colloidal anhydrous silica, glycerol, hypromellose, lactose, macrogol 6000, magnesium stearate, povidone, titanium dioxide.

DESCRIPTION

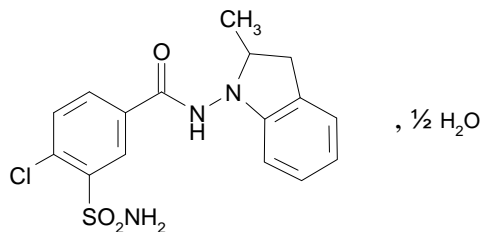
Indapamide hemihydrate (4-chloro-N(2-methyl-1-indolinyl)-3-sulphamoyl benzamide hemihydrate) is a non thiazide indole derivative of chlorosulphonamide. The active ingredient is a racemic mixture. Indapamide is a white crystalline lipophilic powder, soluble in methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene and practically insoluble in water.

CAS Registered Number : 26 807-65-8

Molecular Weight : 374.85 (Indapamide hemihydrate)

Melting point : approximately 185°C

Chemical structure : $C_{16}H_{16}ClN_3O_3S, \frac{1}{2} H_2O$



Mode of Action

Indapamide is an oral antihypertensive agent. The mechanism whereby indapamide exerts its antihypertensive action has not been completely elucidated ; both vascular and renal actions have been implicated. The possible beneficial pharmacological effects of indapamide in the treatment of hypertension include a reduction in cardiac hypertrophy and a reduction in the thickening of arterial walls, a prevention of the accumulation of the embryonic isoform of fibronectin in coronary vessels, free radical scavenging leading to stimulation of vasodilator eicosanoid formation, and interaction with renal carbonic anhydrase.

The renal effects of Natrilix SR (sustained release film-coated tablet containing 1.5 mg of indapamide hemihydrate) are minimal and the antihypertensive effect of indapamide has been attributed to a reduction in vascular reactivity to pressor amines. The finding that indapamide retains its antihypertensive activity to functionally anephric patients lends support to the hypothesis.

The renal site of action of indapamide is the proximal segment of the distal tubule. Indapamide appears to have natriuretic properties (sodium and chloride being excreted in equivalent amounts) with less effect on kaliuresis or uric acid excretion. Only at doses greater than 1.5 mg indapamide hemihydrate sustained release tablet / day is an appreciable increase in urinary volume observed in man. No significant changes in plasma sodium levels have been observed in clinical studies. Significant hypokalaemia (plasma potassium < 3.2 mmol/L) has been reported in 4 % of patients.

Natrilix SR (one tablet daily) does not adversely affect serum triglycerides, LDL cholesterol, the LDL-HDL cholesterol ratio, or glucose tolerance.

PHARMACOKINETIC PROPERTIES

Indapamide hemihydrate 1.5 mg is supplied in a sustained release dosage based on a matrix system in which the active ingredient is dispersed in a support which allows sustained release of indapamide. Indapamide's kinetics are linear.

Absorption

The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract.

Ingestion with food slightly increases the rate and extent of absorption. These changes are unlikely to be clinically significant.

Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between 2 doses.

Distribution

Indapamide is widely distributed throughout the body, with extensive binding to some specific sites. In blood, it is highly bound to red blood cells (80 %) and, more specifically, to carbonic anhydrase (98 %) without having any significant inhibiting activity on this enzyme.

Binding of indapamide to plasma proteins is 79 %.

The plasma elimination half-life is 14 to 24 hours (mean 18 hours).

The drug has a volume of distribution of approximately 60 L.

Steady state is achieved after 7 days.

Repeated administration does not lead to accumulation.

Metabolism

The drug is extensively metabolised in the liver, with only 5 to 7 % of the dose excreted in the urine as unchanged drug.

Elimination is essentially urinary (70 % of the dose) and faecal (22 %) in the form of inactive metabolites.

High risk individuals

In patients with severe renal impairment, plasma concentrations sometimes increase significantly.

INDICATIONS

Management of essential hypertension. It may be tried as a sole therapeutic agent in the treatment of mild to moderate hypertension. Normally, Natrilix SR is used as the initial agent in multiple drug regimes.

CONTRAINDICATIONS

Anuria, progressive and severe oliguria, hepatic coma. Known hypersensitivity to indapamide or to other sulphonamide derivatives.

WARNINGS

Electrolyte changes observed with indapamide hemihydrate become more prominent at doses above 1.5 mg sustained release tablet / day. The daily maximum recommended dose of indapamide hemihydrate is 1.5 mg administered as one sustained release tablet, since doses above 1.5 mg only increase the diuretic effect and electrolyte disturbances consequent to diuresis without any further appreciable antihypertensive effect.

Hypokalaemia may occur at all doses (symptoms of hypokalaemia include weakness, cramps, and cardiac dysrhythmias. Hypokalaemia is a particular hazard in digitalised patients ; dangerous or fatal arrhythmias may be precipitated). Although indapamide hemihydrate as 1.5 mg sustained release tablet daily can be safely administered to hypertensive patients with impaired renal function, caution should be observed when the drug is administered to patients with severe renal impairment since the unchanged drug is excreted primarily by the renal route, and plasma concentrations are elevated in these patients (see Pharmacokinetics).

Hyperuricaemia may occur during administration of indapamide. Rarely gout has been reported.

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

PRECAUTIONS

Patients receiving indapamide should be monitored for signs and symptoms of fluid or electrolyte imbalance ; namely hyponatraemia, hypochloraemia and hypokalaemia. Blood urea, nitrogen and uric acid should also be assessed during therapy. Hypokalaemia will be more common in association with concomitant steroid or ACTH therapy and with inadequate electrolyte intake.

The signs of electrolyte imbalance are dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Special caution should be used in treating patients with severe hepatic disease to avoid metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When Natrilix SR is given with other non diuretic antihypertensive agents, the effects on blood pressure are additive.

Sulphonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. Serious allergic skin reactions (such as Stevens-Johnson syndrome) have also occasionally been reported associated with sulphonamides. These possibilities should be kept in mind with the use of indapamide.

Although one indapamide hemihydrate 1.5 mg sustained release tablet daily can safely be administered to hypertensive patients with impaired renal function, the treatment should be discontinued if increasing azotaemia and oliguria occur.

A study in patients with impaired renal function demonstrated that patients with severe renal impairment (creatinine clearance 11-35 mLs/min) had impaired clearance of indapamide and elevated plasma levels of the drug.

CARCINOGENICITY, MUTAGENICITY, IMPAIRMENT OF FERTILITY.

Carcinogenicity studies in mice and rats showed no evidence of tumourigenicity when indapamide was administered in the diet at levels up to 100 mg/kg/day.

Indapamide was negative in mutagenicity tests in bacteria and in a bone marrow micronucleus test in mice.

A reproduction study in rats showed no impairment of male or female fertility at oral indapamide doses up to 25 mg/kg/day, however, the number of implantation sites was reduced at the highest dose. There was a decrease in weight gain of the F1 generation from rats treated orally at 2.5 mg/kg/day. Galactopoiesis was affected in the F1 generation from rats treated orally at 0.5 mg/kg/day and this led to increased mortality of the F2 generation during the first 48 hours of life. No embryo-foetal toxicity nor teratogenic potential were seen in rats (up to 150 mg/kg/day) and in rabbits (up to 180 mg/kg/day).

USE IN PREGNANCY (CATEGORY C)

Thiazides, related diuretics and loop diuretics enter the fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics like furosemide and bumetanide are probably also associated with this risk. During the latter part of pregnancy products of this type should only be given on sound indications, and then in the lowest effective dose.

There is no information on the use of indapamide in pregnancy. Whilst animal studies have not suggested any teratogenic effect, indapamide is not recommended for administration to pregnant women unless the expected benefit outweighs the potential risk.

USE IN LACTATION

It is not known whether indapamide is excreted in breast milk. It is therefore not recommended that the drug be given to lactating women as the possible effect on the newborn is unknown.

USE IN CHILDREN

Safety and effectiveness have not been established.

ADVERSE REACTIONS

In general, most adverse effects are mild and transient with the most frequently reported being asthenia, dizziness, headache, fatigue, muscle cramps and gastrointestinal disturbances usually occurring within the first month of treatment. Other adverse reactions have been non-specific. Cutaneous rash and impotence have been occasionally reported. Percentages shown below indicate the incidence in clinical trials.

The most severe and common adverse effect is hypokalaemia :

- serum potassium < 3.4 mmol/L : 10 % ;
- serum potassium < 3.2 mmol/L : 4 % (potassium supplementation may be required in up to 7 % of cases).

Central Nervous System (13.1%). Incidence > 1 % and < 5 % : headache, dizziness, fatigue.
Incidence < 1 % : drowsiness, sleepiness, insomnia, weakness, anxiety, visual disturbance.

Gastrointestinal (1.6 %). Incidence < 1% : dryness of mouth, dyspepsia, constipation, abdominal pain.

Musculoskeletal (1.6 %) : Muscle cramps.

Cardiovascular (2.7 %) : Palpitations, chest pain.

Urogenital (0.8 %) : Cystitis.

Dermatological (0.8 %) : Rash, pruritus.

Laboratory abnormalities. Hyperuricaemia (0.4 %). Hyperglycaemia (0.4 %)

Other adverse reactions, reported in clinical studies with the immediate release formulation of indapamide, and not seen in Natrilix SR studies, include the following :

Central Nervous System : vertigo, lethargy.

Gastrointestinal : nausea/anorexia, gastralgia, vomiting, diarrhoea.

Musculoskeletal : joint pain, back pain, weakness of legs.

Cardiovascular : orthostatic hypotension, tachycardia, ECG changes (non specific ST-T changes, U waves, left ventricular strain).

Urogenital : modification of libido, polyuria.

Endocrine : gout.

Other : tinnitus, malaise/fainting, sweat.

Laboratory abnormalities : BUN increase, blood creatinine increase, hypochloraemia, hyponatraemia.

INTERACTIONS

No interactions have been reported between indapamide and oral hypoglycaemic agents, anticoagulants, uricosurics and anti-inflammatory agents. It is recommended that the drug not be used in combination with a diuretic agent since the combination may produce hypokalaemia and hyperuricaemia.

Overdosage Symptoms

There have been no reports of overdosage. Based on the pharmacological activities of indapamide, overdosage may lead to excessive diuresis with electrolyte depletion. In cirrhotic patients, overdosage might precipitate hepatic coma.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Discontinue drug ; induce emesis or perform gastric lavage ; correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

DOSAGE AND ADMINISTRATION

Adults

1 sustained release coated tablet (1.5 mg indapamide hemihydrate) daily to be taken, by oral route, in the morning. The tablet should be swallowed whole and must not be chewed or crushed. The action of Natrilix SR is progressive and whilst the optimum reduction in blood pressure is usually seen after four weeks, a further small but useful reduction in blood pressure may be observed over the following four to six weeks. A larger dose than 1 tablet of Natrilix SR daily is not recommended as there is little additional antihypertensive effect, whilst the diuretic effect becomes more prominent.

A single daily tablet of Natrilix SR may effectively be combined with the following antihypertensive agents : beta-blockers, methyldopa, clonidine, prazosin and ACE inhibitors.

Combination with a diuretic agent is not recommended as significant electrolyte disturbances may ensue. Indapamide has a slight but significant carry-over hypotensive effect lasting up to 1 or 2 weeks after the cessation of therapy.

PRESENTATION

White sustained release film-coated biconvex tablet containing indapamide hemihydrate 1.5 mg.

Natrilix SR is supplied in boxes containing 30 or 90 tablets. Tablets are in blister platforms of 30.*

STORAGE

Store in a dry place below 25 °C

POISONS SCHEDULE

S4 – Prescription-only Medicine

AUSTRALIA SPONSOR

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