AUSTRALIAN PRODUCT INFORMATION
NATRILIX SR (INDAPAMIDE HEMIHYDRATE) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Indapamide hemihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NATRILIX SR tablet contains 1.5 mg of sustained release indapamide hemihydrate.

Excipient with known effect: lactose monohydrate. For the full list of excipients, see *section 6.1* - List of excipients.

3 PHARMACEUTICAL FORM

Each NATRILIX SR tablet is a white, film-coated biconvex tablet containing sustained release indapamide hemihydrate 1.5 mg.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of hypertension. It may be tried as a sole therapeutic agent in the treatment of hypertension. Normally, NATRILIX SR is used as the initial agent in multiple drug regimes.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults. One NATRILIX SR tablet 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 one tablet of NATRILIX SR daily is not recommended as there is little additional antihypertensive effect, whilst the diuretic effect becomes more pronounced.

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

Combination with a diuretic is not recommended as significant electrolyte disturbances may occur. Indapamide has a slight but significant carry-over hypotensive effect lasting up to one or two weeks after treatment is stopped.

4.3 CONTRAINDICATIONS

NATRILIX SR is contraindicated in:

- Severe renal failure, anuria, progressive and severe oliguria.
- Hepatic coma, hepatic encephalopathy or severe impairment of liver function.
- Known hypersensitivity to indapamide, other sulphonamide derivatives, or any of the excipients (see *section 6.1 – List of excipients*).
- Hypokalaemia.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Electrolyte changes observed with indapamide hemihydrate become more pronounced at doses above 1.5mg sustained release tablet / day. The daily maximum recommended dose of NATRILIX SR is one tablet/ day, since doses above this increase the diuretic effect and electrolyte disturbances, 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 patients treated with digoxin as dangerous or fatal arrhythmias may be precipitated. Although NATRILIX SR can be safely administered to hypertensive patients with renal impairment, caution should be observed when it is administered to patients with severe renal impairment. In this case the unchanged drug is excreted primarily by the renal route, and plasma concentrations are elevated (see *section 5.2 - Pharmacokinetic properties*).

Precautions

Hepatic encephalopathy

When liver function is impaired, thiazide-related diuretics may cause, particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma. Administration of the diuretic must be stopped immediately if this occurs.

Uric acid

Hyperuricaemia may occur during treatment with indapamide, and gout has been reported rarely. Tendency to gout attacks may be increased in patients with hyperuricaemia.

Lithium

Diuretics should not be given with lithium because they reduce its renal clearance and add a high risk of lithium toxicity (see *section 4.5 - Interactions with other medicines and other forms of interactions)*.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. It is recommended to stop treatment if a photosensitivity reaction occurs during treatment. If re-administration of the diuretic is deemed necessary, it is recommended that areas exposed to the sun or to artificial UVA are protected.

Lactose intolerance

NATRILIX SR tablets contain lactose monohydrate.

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

Water and electrolyte balance

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 treatment. 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.

Plasma sodium

This must be measured before starting treatment, then subsequently at regular intervals. The decrease in plasma sodium may initially be asymptomatic. Regular monitoring is therefore essential and should be more frequent in the elderly and in patients with cirrhosis (see *section 4.8 - Adverse effects (Undesirable effects*)). Treatment with any diuretic may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis.

Plasma potassium

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. Hypokalaemia may cause muscle disorders. Cases of rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of hypokalaemia (<3.4 mmol/L) must be prevented in certain high risk populations, i.e. the elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, and patients with coronary artery disease and/or heart failure. In these patients, hypokalaemia increases the cardiac toxicity of digitalis preparations and increases the risk of arrhythmias.

Hypokalaemia will be more common when combined with a steroid or adrenocorticoptropic (ACTH) treatment and when electrolyte intake is inadequate.

Individuals with a long QT interval, whether the origin is congenital or iatrogenic, are also at increased risk as hypokalaemia and bradycardia, are predisposing factors to the onset of severe arrhythmias, in particular, potentially fatal *Torsades de pointes*.

Plasma potassium should be measured in the first week of treatment. More frequent monitoring of plasma potassium is required in all the situations indicated above.

Hypokalaemia, if detected, should be corrected. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

Plasma magnesium

Thiazides and related diuretics have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see *section 4.5 - Interactions with other medicines and other forms of interactions and 4.8 - Adverse effects (Undesirable effects*)).

Plasma calcium

Diuretic treatment should be withdrawn before the investigation of parathyroid function. Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

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

When NATRILIX SR is combined with other non-diuretic antihypertensive medicines, the effects on blood pressure are additive.

Sulfonamide 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 with sulfonamides. This should be considered when using indapamide.

Although a NATRILIX SR dose of one tablet/ day can be used safely in patients with hypertension and renal impairment, treatment should be discontinued if there is an increase in azotaemia and oliguria.

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

Blood glucose

Monitoring of blood glucose is important in patients with diabetes, in particular in the presence of hypokalaemia.

Athletes

NATRILIX SR contains indapamide which may give a positive reaction in doping tests.

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.

Use in the elderly

In the elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated with NATRILIX SR when renal function is normal or only minimally impaired.

Paediatric use

Safety and effectiveness have not been established.

Effects on laboratory tests

Hyperuricaemia (0.4 %). Hyperglycaemia (0.4 %) (see *section 4.8 - Adverse effects (Undesirable effects*)).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interactions have been reported between indapamide and anticoagulants, or between indapamide and uricosuric medicines. It is recommended that NATRILIX SR not be used in combination with a diuretic since the combination may cause hypokalaemia and hyperuricaemia.

Combined use which is NOT RECOMMENDED:

Lithium

The combined use of NATRILIX SR and lithium may result in increased plasma lithium levels and symptoms of overdose (due to decreased urinary lithium excretion). If diuretics are necessary, careful monitoring of plasma lithium and dose adjustment are required.

Combined use which REQUIRES SPECIAL CARE:

Torsades de pointes-inducing drugs

The combined use of NATRILIX SR and *Torsades de pointes*-inducing drugs, including the following, is not recommended due to the increased risk of ventricular arrhythmias, particularly *Torsades de pointes* (hypokalaemia is a risk factor). Medicines which induce *Torsade de pointes* include (but are not limited to):

- class Ia antiarrhythmic agents (e.g. disopyramide) and class Ic antiarrhythmic agents (e.g. flecainide)
- class III antiarrhythmic agents (e.g. amiodarone, sotalol)
- some antipsychotics : phenothiazines (e.g. chlorpromazine, trifluoperazine), benzamides (e.g. amisulpride, sulpiride), butyrophenones (e.g. droperidol, haloperidol) and other antipsychotics
- psychoanaleptic (e.g. donepezil)
- some antidepressants (e.g. citalopram, escitalopram)
- antimicrobial agents: fluoroquinolones (e.g. moxifloxacin, ciprofloxacin), macrolides (e.g. erythromycin IV, clarithromycin), azole antifungals (e.g. fluconazole)
- antiparasitics (e.g. chloroquine, pentamidine)
- antihistamines
- antiemetics (e.g. ondansetron, domperidone)
- antineoplastic and immunomodulating agents (e.g. vandetanib, oxaliplatin, anagrelide)
- anaesthetics (e.g. propofol, sevoflurane).
- others: diphemanil, methadone, papaverine, cilostazol

This list is indicative and not exhaustive.

Monitor (using plasma electrolytes and ECG) for hypokalaemia and correct, if required, before using NATRILIX SR and a *Torsades de pointes*-inducing drug in combination.

NSAIDs (systemic route) including COX-2 selective inhibitors, high dose acetylsalicylic acid (≥ 3 g/day)

Due to the risk of acute renal failure in patients with dehydration as a result of decreased glomerular filtration, it is recommended that hydration and renal function be monitored at the start of treatment. Combined use with NSAIDs may also result in a reduction in the antihypertensive effect of NATRILIX SR.

Angiotensin converting enzyme (ACE) inhibitors

Combined use with ACE inhibitors in the presence of pre-existing sodium depletion (particularly in patients with renal artery stenosis) may increase the risk of sudden hypotension and/or acute renal failure.

In patients with hypertension when prior diuretic treatment may have caused sodium depletion, it is necessary to either:

- stop the diuretic three days before starting treatment with the ACE inhibitor, and restart a hypokalaemic diuretic if necessary; or
- give low initial doses of the ACE inhibitor and increase the dose gradually.

In patients with congestive heart failure, initiation with a very low dose of ACE inhibitor, possibly after a reduction in the dose of the hypokalaemic diuretic, is recommended.

The monitoring of renal function (plasma creatinine) during the first weeks of treatment with an ACE inhibitor is recommended in all patients.

Other compounds causing hypokalaemia: amphotericin B (amphotericin) (IV), gluco- and mineralo-corticoids (systemic route), stimulant laxatives

Due to the increased risk of hypokalaemia (additive effect):

- monitoring, and correction if required, of plasma potassium (especially during treatment with digoxin) is recommended
- the use of non-stimulant laxatives is recommended.

Baclofen

Due to the increased risk of antihypertensive effects, it is recommended that hydration and renal function be monitored at the start of treatment.

Digitalis preparations

Monitoring of plasma potassium, plasma magnesium and ECG is recommended during treatment with digitalis, and if necessary, adjust the treatment as hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis.

Allopurinol

Combined use with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Combinations to be taken into CONSIDERATION:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene)

Due to the increased risk of either hyperkalaemia or hypokalaemia (particularly in patients with renal failure or diabetes), care should be taken when co-administering potassium-sparing diuretics. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin

Do not co-administer with metformin when plasma creatinine exceeds 15 mg/L (135 µmol/L) in men and 12 mg/L (110 µmol/L) in women due to the increased risk of metformin induced lactic acidosis as a result of the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics.

Iodinated contrast media

Adequate hydration before administration of the iodinated compound is recommended due to an increased risk of acute renal failure resulting from dehydration, particularly when large doses of iodinated contrast media are used.

Imipramine-like antidepressants, neuroleptics

Caution is recommended with these combinations due to an increased antihypertensive effect and increased risk of orthostatic hypotension.

Calcium (salts)

Caution is recommended with this combination due to the risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Cyclosporin, tacrolimus

Caution is recommended with this combination due to the risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (tetracosactrin) (systemic route)

Caution is recommended with this combination due to the risk of decreased antihypertensive effect (water/sodium retention due to corticosteroids).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

A reproductive toxicity 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.

Use in pregnancy – Pregnancy Category C

Indapamide should be avoided in pregnant women and should not be used to treat oedema in pregnancy. There are limited data with the use of indapamide in pregnant women. Prolonged exposure to thiazides during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause foetal-placental ischaemia and growth retardation.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopaenia has been reported with thiazides and related diuretics. Loop diuretics like furosemide (frusemide) and bumetanide are probably also associated with this risk. During the latter part of pregnancy, medicines of this type should be used with caution and at the lowest effective dose.

Use in lactation.

Indapamide should not be used during breast-feeding. Indapamide is excreted in human breast milk and the possible effect on the newborn is unknown and cannot be excluded. Indapamide is closely related to thiazide diuretics which have associated with a decrease in, or even suppression of, lactation. Hypersensitivity to sulfonamide-derived medicines and hypokalaemia might occur.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Indapamide does not affect vigilance but different reactions related to a decrease in blood pressure may occur in individual cases, especially at the start of treatment or when another antihypertensive agent is added. Treatment with any blood pressure lowering agent may, therefore, affect the ability to drive, cross the road safely or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

In general, most adverse effects are mild and transient. The most frequently reported are: hypokalaemia, hypersensitivity reactions, mainly dermatological (in subjects with a predisposition to allergic and asthmatic

reactions and macropapular rashes), asthenia, dizziness, headache, fatigue, muscle cramps and gastrointestinal disturbances. These usually occur within the first month of treatment.

During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/L) was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after four to six weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l. Hypochloraemia 9.4%; hyponatraemia 3.1 %.

The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent.

Other adverse reactions have been nonspecific. Cutaneous rash and impotence have been occasionally reported. Percentages shown below indicate the incidence in clinical trials.

The following adverse effects have been observed with indapamide during treatment ranked according to the following frequencies: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1.000, < 1/100); rare (≥ 1/10.000); very rare (<1/10.000); not known (cannot be estimated from the available data):

MedDRA System Organ Class	**Adverse Effects**	**Frequency**
Blood and the lymphatic System Disorders	Agranulocytosis	Very rare
	Aplastic anaemia	Very rare
	Haemolytic anaemia	Very rare
	Leucopenia	Very rare
	Thrombocytopenia	Very rare
Metabolism and Nutrition Disorders	Hypercalcaemia	Very rare
	Hypochloraemia	Rare
	Hypomagnesaemia	Rare
	Hypokalaemia (see *section 4.3 - Contraindications and section 4.4 - Special warnings and precautions for use)*	Common
	Hyponatraemia† (see *section 4.4 - Special warnings and precautions for use*)	Uncommon
Nervous System disorders	Vertigo	Rare
	Fatigue	Common
	Headache	Common
	Dizziness	Common
	Paresthesia	Rare
	Syncope§	Not known
	Drowsiness	Uncommon
	Sleepiness	Uncommon
	Insomnia	Uncommon
	Anxiety	Uncommon
	Weakness	Uncommon
Eye disorders	Visual impairment	Uncommon
	Blurred vision§	Not known
	Myopia§	Not known
	Acute angle-closure glaucoma§	Not known
	Choroidal effusion§	Not known

MedDRA System Organ Class	Adverse Effects	Frequency
Cardiac Disorders	Arrhythmia	Very rare
	Torsade de pointes (potentially fatal)§ (see *section 4.4 - Special warnings and precautions for use* and *section 4.5 - Interactions with other medicines and other forms of interactions*)	Not known
	Palpitations	Very rare
	Chest pain	Very rare
Vascular Disorders	Hypotension	Very rare
Gastrointestinal Disorders	Vomiting	Uncommon
	Dyspepsia	Uncommon
	Abdominal pain	Uncommon
	Nausea	Rare
	Constipation	Rare
	Dry mouth	Rare
	Pancreatitis	Very rare
Hepatobiliary Disorders	Abnormal hepatic function	Very rare
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency§ (see *section 4.3 -Contraindications* and *section 4.4 - Special warnings and precautions for use*)	Not known
	Hepatitis§	Not known
Skin and Subcutaneous Tissue Disorder	Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions	Common
	Maculopapular rashes	Common
	Purpura	Uncommon
	Pruritis	Uncommon
	Angioedema	Very rare
	Urticaria	Very rare
	Toxic epidermic necrolysis	Very rare
	Stevens-Johnson Syndrome	Very rare
	Possible worsening of pre-existing acute disseminated lupus erythematosus§	Not known
	Photosensitivity reactions§ (see *section 4.4 -Special warnings and precautions for use*)	Not known
Musculoskeletal Disorders and Connective Tissue Disorders	Muscle cramps	Common
	Muscle spasms§	Not known
	Muscular weakness§	Not known
	Myalgia§	Not known
	Rhabdomyolysis§	Not known
Renal and Urinary Disorders	Renal failure	Very rare
	Cystitis	Uncommon

MedDRA System Organ Class	Adverse Effects	Frequency
Reproductive system and Breast disorders	Erectile dysfunction§	Uncommon
Investigations	Electrocardiogram QT prolonged§ (see *section 4.4 - Special warnings and precautions for use* and *section 4.5 - Interactions with other medicines and other forms of interactions*)	Not known
	Blood glucose increased§‡ (see *section 4.4 - Special warnings and precautions for use*)	Not known
	Blood uric acid increased§‡ (see s*ection 4.4 - Special warnings and precautions for use*)	Not known
	Elevated liver enzyme levels§	Not known

† Reported in clinical studies with the immediate release formulation of indapamide, and not seen in NATRILIX SR studies

§ Reported for indapamide as a post-marketing adverse effect

‡ Appropriateness of treatment with NATRILIX SR must be very carefully weighed in patients with gout or diabetes.

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

Central Nervous System: lethargy.

Gastrointestinal: anorexia, gastralgia, diarrhoea.

Metabolism and nutrition disorders: hypochloraemia, hyponatraemia.

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

Cardiac disorders: tachycardia, ECG changes (non-specific ST-T changes, U waves, left ventricular strain).

Urogenital: modification of libido, polyuria.

Vascular disorders: orthostatic hypotension.

Endocrine: gout.

Other: tinnitus, malaise/fainting, sweat.

Laboratory abnormalities: BUN increase, blood creatinine increase.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Signs of acute poisoning at higher doses take the form of water/electrolyte disturbances (hyponatraemia, hypokalaemia) and may include the possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia). In patients with cirrhosis, an overdose might precipitate hepatic coma.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive. Discontinue drug; induce emesis or perform gastric lavage and/or administration of activated charcoal (activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected), correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Indapamide is an oral antihypertensive medicine. 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 in patients who are functionally anephric lends support to this 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.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

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 two doses.

Distribution

Indapamide is widely distributed throughout the body, with extensive binding to specific sites. In blood, it is highly bound to red blood cells (80 %) and, more specifically, to carbonic acid 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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

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

Mutagenicity

Indapamide was negative in mutagenicity tests in bacteria, and bone marrow micronucleus tests in mice. 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 or teratogenic potential were seen in rats (up to 150 mg/kg/day) and in rabbits (up to 180 mg/kg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Colloidal anhydrous silica, glycerol, hypromellose, lactose monohydrate, macrogol 6000, magnesium stearate, povidone, titanium dioxide.

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 in a dry place below 25 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

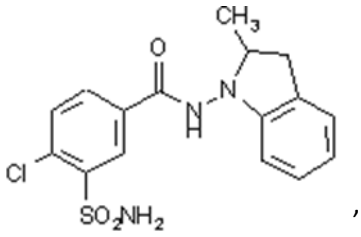
NATRILIX SR is supplied in boxes containing 10[#], 30 or 90 tablets. Tablets are in blister platforms of 30.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Indapamide hemihydrate (4-chloro-N(2-methyl-1-indolinyl)-3- sulfamoyl benzamide hemihydrate) is a non-thiazide indole derivative of chlorosulfonamide. 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.



, ½ H_2O

CAS number:

26 807-65-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Servier Laboratories (Aust.) Pty. Ltd.
www.servier.com.au
Level 4, Building 9
588A Swan Street
Burnley, 3121, Victoria

9 DATE OF FIRST APPROVAL

7 December 1998

10 DATE OF REVISION

7 July 2022

[#] The 10 tablet pack is not supplied in Australia

Summary table of changes

Section(s) Changed	Summary of new information
8	Change of Sponsor address