NATRILIX® SR

Indapamide 1.5 mg

Composition
Each sustained release coated tablet contains:
Indapamide …… 1.5 mg

Therapeutic indications
Natrilix SR is indicated in essential hypertension in adults.

Posology and method of administration
Posology
One sustained release tablet per 24 hours, preferably in the morning, to be swallowed whole with water and not chewed.

At higher doses the antihypertensive action of indapamide is not enhanced but the saluretic effect is increased.

In case one or several doses have been missed: do not take a double dose the day after the omitted doses.

Special populations

Renal impairment (see sections "Contraindications" and "Special warnings and precautions for use"):
In severe renal failure (creatinine clearance below 30 ml/min), treatment is contraindicated.
Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired.

Hepatic impairment (see sections "Contraindications" and "Special warnings and precautions for use"):
In severe hepatic impairment, treatment is contraindicated.

Elderly (see section "Special warnings and precautions for use"):
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 population:
The safety and efficacy of Natrilix SR in children and adolescents have not been established. No data are available.

Method of administration
Oral use

Contraindications

- Hypersensitivity to the active substance, or to other sulfonamides.
- Severe renal failure.
- Hepatic encephalopathy or severe impairment of liver function.
- Hypokalaemia.
- Recent cerebrovascular accident

Special warnings and precautions for use

Special warnings

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.

Photosensitivity:
Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section "Undesirable effects"). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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

Special precautions for use

Water and electrolyte balance:

- Plasma sodium:
  This must be measured before starting treatment, then at regular intervals subsequently. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients (see sections "Undesirable effects" and "Overdose"). Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible of dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.

- 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, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

  Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal *torsades de pointes*.

  More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment. Detection of hypokalaemia requires its correction. 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 including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section "Interactions with other medicinal products and other forms of interaction" and "Undesirable effects").

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

Blood glucose:

Monitoring of blood glucose is important in diabetics, in particular in the presence of hypokalaemia.

Uric acid:
Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics:
Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25 mg/l, i.e. 220 μmol/l in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.
Hypovolaemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and plasma creatinine. This transitory functional renal insufficiency is of no consequence in individuals with normal renal function but may worsen preexisting renal insufficiency.

Athletes:
The attention of athletes is drawn to the fact that this medicinal product contains a drug substance, 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.

Breast-feeding
Natrilix SR is excreted into human milk in small amounts, and when given at high doses during breast-feeding is not recommended, because it can inhibit the milk production. Using Natrilix SR in breast-feeding women should be kept as low as possible.

Interactions with other medicinal products and other forms of interaction

Combinations that are not recommended:

Lithium:
Increased plasma lithium with signs of overdosage, as with a salt-free diet (decreased urinary lithium excretion). However, if the use of diuretics is necessary, careful monitoring of plasma lithium and dose adjustment are required.

Combinations requiring precautions for use:

Torsades de pointes-inducing drugs such as but not limited to:
- class Ia antiarrhythmic agents (e.g quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmic agents (e.g amiodarone, sotalol, dofetilide, ibutilide, bretylium),
- some antipsychotics:

phenothiazines (e.g chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
benzamides (e.g amisulpride, sulpiride, sultopride, tiapride),
butyrophenones (e.g droperidol, haloperidol),
other antipsychotic (e.g pimozide),
other substances: (e.g bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV, methadone, astemizole, terfenadine).
Increased risk of ventricular arrhythmias, particularly *torsades de pointes* (hypokalaemia is a risk factor).
Monitor for hypokalaemia and correct, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.

Use substances which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.

N.S.A.I.Ds. (systemic route) including COX-2 selective inhibitors, high dose acetylsalicylic acid (≥ 3 g/day):
Possible reduction in the antihypertensive effect of indapamide.
Risk of acute renal failure in dehydrated patients (decreased glomerular filtration). Hydrate the patient; monitor renal function at the start of treatment.

Angiotensin converting enzyme (A.C.E.) inhibitors:
Risk of sudden hypotension and/or acute renal failure when treatment with an A.C.E. inhibitor is initiated in the presence of preexisting sodium depletion (particularly in patients with renal artery stenosis).

In hypertension, when prior diuretic treatment may have caused sodium depletion, it is necessary:
- either to stop the diuretic 3 days before starting treatment with the A.C.E. inhibitor, and restart a hypokalaemic diuretic if necessary;
- or give low initial doses of the A.C.E. inhibitor and increase the dose gradually.

In congestive heart failure, start with a very low dose of A.C.E. inhibitor, possibly after a reduction in the dose of the concomitant hypokalaemic diuretic.

In all cases, monitor renal function (plasma creatinine) during the first weeks of treatment with an A.C.E. inhibitor.

Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives:
Increased risk of hypokalaemia (additive effect).
Monitoring of plasma potassium and correction if required. Must be particularly borne in mind in case of concomitant digitalis treatment. Use non-stimulant laxatives.

Baclofen:
Increased antihypertensive effect.
Hydrate the patient; monitor renal function at the start of treatment.

Digitalis preparations:
Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis.
Monitoring of plasma potassium, magnesium and ECG and, if necessary, adjust the treatment.

Combinations requiring special care:

Allopurinol:
Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Combinations to be taken into consideration:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene):
Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia (particularly in patients with renal failure or diabetes) may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin:
Increased risk of metformin-induced lactic acidosis due to the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics.
Do not use metformin when plasma creatinine exceeds 15 mg/l (135 μmol/l) in men and 12 mg/l (110 μmol/l) in women.

Iodinated contrast media:

In the presence of dehydration caused by diuretics, increased risk of acute renal failure, in particular when large doses of iodinated contrast media are used.
Rehydration before administration of the iodinated compound.

Imipramine-like antidepressants, neuroleptics:
Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Calcium (salts):
Risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Ciclosporin, tacrolimus:
Risk of increased plasma creatinine without any change in circulating ciclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (systemic route):
Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women. Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a feto-placental ischaemia and growth retardation.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section "Preclinical safety data").

As a precautionary measure, it is preferable to avoid the use of Indapamide during pregnancy.

Breast-feeding
There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulphonamide-derived medicines and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded.
Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of milk lactation.

Indapamide is not recommended during breast-feeding.

Fertility
Reproductive toxicity studies showed no effect on fertility in female and male rats (see section "Preclinical Safety Data"). No effects on human fertility are anticipated.

Effects on ability to drive and use machines

Indapamide does not affect vigilance but different reactions in relation with the decrease in blood pressure may occur in individual cases, especially at the start of the treatment or when another antihypertensive agent is added.
As a result the ability to drive vehicles or to operate machinery may be impaired.

Undesirable effects

Summary of safety profile
The most commonly reported adverse reactions are hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

Tabulated summary of adverse reactions

The following undesirable effects have been observed with indapamide during treatment ranked under the following frequency:

Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to <1/1,000); very rare (≥1/100,000 to <1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable 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	Hypokalaemia (see section "Special warnings and precautions for use")	Common
	Hyponatraemia (see section "Special warnings and precautions for use")	Uncommon
	Hypochloraemia	Rare
	Hypomagnesaemia	Rare
	Hypercalcaemia	Very rare
Nervous System disorders	Vertigo	Rare
	Fatigue	Rare
	Headache	Rare
	Paresthesia	Rare
	Syncope	Not known
Eye disorders	Myopia	Not known
	Blurred vision	Not known
	Visual impairment	Not known
	Acute angle-closure glaucoma	Not known
	Choroidal effusion	Not known
Cardiac Disorders	Arrhythmia	Very rare
	Torsade de pointes (potentially fatal) (see sections "Special warnings and precautions for use" and "Interactions with other medicinal products and other forms of interaction")	Not known
Vascular Disorders	Hypotension	Very rare
Gastrointestinal Disorders	Vomiting	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 sections "Contraindications" and "Special warnings and precautions for use")	Not known
	Hepatitis	Not known
Skin and Subcutaneous Tissue Disorder	Hypersensitivity reactions	Common
	Maculopapular rashes	Common
	Purpura	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 "Special warnings and precautions for use")	Not known
Renal and Urinary Disorders	Renal failure	Very rare
Musculoskeletal and Connective Tissue Disorders	Muscle spasms	Not known
	Muscular weakness	Not known
	Myalgia	Not known
	Rhabdomyolysis	Not known
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
Investigations	Electrocardiogram QT prolonged (see sections "Special warnings and precautions for use" and "Interactions with other medicinal products and other forms of interaction")	Not known
	Blood glucose increased (see section "Special warnings and precautions for use")	Not known
	Blood uric acid increased (see section "Special warnings and precautions for use")	Not known
	Elevated liver enzyme levels	Not known

Description of selected adverse reactions
During phase II and III studies of indapamide 1.5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:
-Indapamide 1.5mg: Plasma potassium <3.4 mmol/l was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.

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 e-meso subsite at https://e-meso.pom.go.id or report to Pusat Farmakovigilans/MESO Nasional, Badan Pengawas Obat dan Makanan (BPOM) : Phone +62 21 4244 691 Ext. 1079, or email at pv-center@pom.go.id.

Overdose

Symptoms
Indapamide has been found free of toxicity at up to 40 mg, i.e. 27 times the therapeutic dose.

Signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatraemia, hypokalaemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).

Management
Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal, followed by restoration of water/electrolyte balance to normal in a specialised centre.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Sulfonamides, plain, ATC code: C 03 BA 11

Mechanism of action
Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Pharmacodynamic effects
Phase II and III studies using monotherapy have demonstrated an antihypertensive effect lasting 24 hours. This was present at doses where the diuretic effect was of mild intensity.

The antihypertensive activity of indapamide is related to an improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance.
Indapamide reduces left ventricular hypertrophy.
Thiazide and related diuretics have a plateau therapeutic effect beyond a certain dose, while adverse effects continue to increase. The dose should not be increased if treatment is ineffective.

It has also been shown, in the short-, mid- and long-term in hypertensive patients, that indapamide:
- does not interfere with lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol;
- does not interfere with carbohydrate metabolism, even in diabetic hypertensive patients.

Pharmacokinetic properties
Indapamide 1.5 mg is supplied in a prolonged release dosage based on a matrix system in which the drug substance is dispersed within a support which allows sustained release of indapamide.

Absorption:
The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract.
Eating slightly increases the rapidity of absorption but has no influence on the amount of the drug absorbed.
Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between 2 doses.
Intra-individual variability exists.

Distribution:
Binding of indapamide to plasma proteins is 79%.
The plasma elimination half-life is 14 to 24 hours (mean 18 hours).
Steady state is achieved after 7 days.
Repeated administration does not lead to accumulation.

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

High risk individuals:
Pharmacokinetic parameters are unchanged in renal failure patients.

Preclinical safety data
Indapamide has been tested negative concerning mutagenic and carcinogenic properties.
The highest doses administered orally to different animal species (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms of poisoning during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, i.e. bradypnoea and peripheral vasodilation.
Reproductive toxicity studies have not shown embryotoxicity and teratogenicity.
Fertility was not impaired either in male or in female rats.

Storage
- Do not exceed the expiry date clearly indicted on the outer packing.
- Store below 30ºC.

Packing
Box of 30 sustained release coated tablets (3 strips of 10 tablets)

ON DOCTOR'S PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

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PT. Darya-Varia Laboratoria Tbk.
Bogor - Indonesia
Reg. No.: DKL1704527296A1

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