SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME

NATRILIX SR sustained release film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION IN ACTIVE SUBSTANCE

Indapamide..... 1.50 mg
Excipients q.s.for one sustained release film-coated tablet

3. DOSAGE FORM

Sustained release film-coated tablet.
Round, white tablet.

4. CLINICAL DATA

4.1 Therapeutic indications

Essential hypertension.

4.2 Dosage and administration

Oral route

One tablet per 24 hours, preferably in the morning.
The tablet should be taken whole with water and should not be chewed.
Higher doses do not improve the antihypertensive action of Indapamide; rather, they increase the salidiuretic effect.

4.3 Contraindications

- Hypersensitivity to sulfonamides
- Severe renal failure
- Hepatic encephalopathy or severe liver failure
- Hypokalemia

4.4 Warnings and special precautions

Warnings

When liver function is impaired, thiazide and related diuretics may cause hepatic encephalopathy. Administration of the diuretic must be stopped immediately if this occurs.

Due to the presence of lactose, this drug is contraindicated in the case of congenital galactosemia, glucose and galactose malabsorption syndrome or lactase deficiency.

Precautions of use

Water and electrolyte balance

- *Plasma sodium*
  This must be measured before starting treatment, then at regular intervals subsequently. Any diuretic treatment may cause hyponatremia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be carried out even more frequently in the elderly and cirrhotic patients (see Side effects and Overdosage).

- *Plasma potassium*
  Potassium depletion with hypokalemia is the major risk of thiazide and related diuretics. The risk of the onset of hypokalemia (< 3.4 mmol/l) must be prevented in certain high-risk populations, i.e. the elderly, malnourished and/or polymedicated, cirrhotic patients with edema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalemia increases the cardiac toxicity of digitalis preparations and the risk of arrhythmias.

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

  More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be carried out during the first week following the start of treatment.
  Detection of hypokalemia should be followed by its correction.

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

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

Uric acid
Tendency to gout attacks may be increased in hyperuricemic 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 value must be adjusted in relation to age, weight and sex.
Hypovolemia, 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 plasma 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 drug contains an active ingredient that may induce a positive reaction during anti-doping control tests.

4.5 Interactions with other medicinal products and other forms of interaction

Inadvisable combination

+ Lithium
Increased blood lithium concentrations with signs of overdosage, as during a sodium-free diet (reduction in urinary lithium excretion). However, if the use of diuretics is required, the blood lithium levels should be strictly monitored and the dosage adjusted.

Combinations requiring precautions

+ Drugs causing wave burst arrhythmias
- Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics:

Phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
Benzamides (amisulpride, sulpiride, sultopride, tiapride),
Butyrophenones (droperidol, haloperidol),
Others: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV.

Increased risk of ventricular arrhythmia, in particular wave burst arrhythmias (hypokalemia is a risk factor).
Hypokalemia should be monitored and corrected if necessary, before starting a combination. Clinical signs, plasma electrolytes and the ECG should be monitored.

Use substances without the disadvantage of causing wave burst arrhythmia in the case of hypokalemia.

+ N.S.A.I.D (systemic), ***including selective COX-2 inhibitors, and high dose salicylates (>3 g/day)***
Possible decrease in the antihypertensive effect of Indapamide.
Risk of acute renal failure in dehydrated patients (decreased glomerular filtration).
Hydrate the patient; monitor the renal function at the start of treatment.

+ Angiotensin converting enzyme (ACE) inhibitors
Risk of sudden hypotension and/or acute renal failure at the start of treatment by a converting enzyme inhibitor if there is preexisting sodium depletion (in particular in patients with renal artery stenosis).

In essential hypertension, when an earlier diuretic treatment may have involved a depletion of sodium, it is necessary to:
. either stop the diuretic 3 days before the start of the ACE inhibitor treatment and reintroduce a potassium-lowering diuretic if necessary ;
. or initially administer low doses of the ACE inhibitor and then increase the dose gradually.

In congestive heart failure, begin with a very low dose of ACE inhibitor possibly after reducing the dose of associated potassium-lowering diuretic.

In all cases, monitor renal function (plasma creatinine) during the first few weeks of treatment with the ACE inhibitor.

+ Other hypokalemic compounds: amphotericin B (IV), gluco- and mineralocorticoids (oral), tetracosactide, stimulant laxatives
Increased risk of hypokalemia (additive effect).
Monitoring of plasma potassium and correction, if required, must be particularly borne in mind in the 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
Hypokalemia predisposes to the toxic effects of digitalis.
Monitor the plasma potassium, ECG and, if necessary, review the treatment.

Combinations to be taken into account

+ Hyperkalemic diuretics (amiloride, spironolactone, triamterene)
In the case of a rational combinations, useful for certain patients, the possibility of hypokalemia or hyperkalemia (in particular in renal failure and diabetic patients) is not eliminated. Monitor plasma potassium and ECG and review treatment if necessary.

+ Metformin
An increased risk of the appearance of lactic acidosis due to metformin, triggered by possible functional renal failure related to diuretics and more particularly to loop diuretics.
Do not use metformin when blood creatinine levels exceed 15 mg/liter (135 micromoles/liter) in men and 12 mg/liter (110 micromoles/liter) in women.

+ Iodinated contrast media
In cases of dehydration caused by diuretics, there is an increased risk of acute renal failure, in particular when high doses of iodinated contrast media are used.
Rehydration before the administration of the iodinated compound.

+ Imipramine antidepressants (tricyclics), neuroleptics
Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

+ Calcium (salts)
Risk of hypercalcemia resulting from decreased urinary calcium elimination.

+ Cyclosporin, Tacrolimus
Risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

+ Corticosteroids, tetracosactide (oral route)
Decreased antihypertensive effect (water/sodium retention of corticosteroids).

4.6 Pregnancy and breast-feeding

Pregnancy
As a general rule, the administration of thiazide and related diuretics should be avoided in pregnant women and should never be used to treat the physiological edema of pregnancy. Diuretics can cause fetoplacental ischemia, with a risk of fetal hypotrophy.

Breast-feeding
Breast-feeding is inadvisable (passage into the breast milk).

4.7 Effects on the ability to drive vehicles and use machinery

NATRILIX SR does not affect alertness, but individual reactions in relation to the decrease in blood pressure may occur in certain patients, especially at the start of treatment or in combination with another antihypertensive drug.
Consequently, the ability to drive vehicles or to use machinery may be diminished.

4.6 Side effects

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

Thiazide and related diuretics, including Indapamide, may cause:

Problems involving the blood and lymphatic system
- Very rare: thrombocytopenia, leucopenia, agranulocytosis, aplastic anemia, hemolytic anemia

Problems involving the nervous system
- Rare: dizziness, fatigue, headaches, paresthesia

Heart problems
- Very rare: arrhythmia, hypotension

Gastro-intestinal problems
- Rare: nausea, constipation, dry mouth
- Very rare: pancreatitis

Hepato-biliary problems
- In the case of liver failure, hepatic encephalopathy may occur (cf. Sections 4.3 Contraindications and 4.4 Special precautions)
- Very rare: altered liver function.

Skin and tissue conditions
- Hypersensitivity reactions, mainly dermatological (common: maculo-papular eruptions, less common: purpura) in subjects predisposed to allergic and asthmatic symptoms.
- Possibility of exacerbation of preexisting acute disseminated lupus erythematosus.

Regarding laboratory parameters

- During clinical trials, hypokalemia was observed: plasma potassium < 3.4 mmol/l in 10% of patients seen and < 3.2 mmol/l in 4% of patients after 4 to 6 weeks' treatment. After 12 weeks' treatment, the mean fall in potassium was 0.23 mmol/l.

- Potassium depletion with hypokalemia, particularly serious in certain at-risk populations (cf. Section 4.4 Special Warnings and Precautions for use).

- Hyponatremia with hypovolemia, responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and the degree of this effect are slight.

- An increase in plasma uric acid and blood glucose during treatment: the indication of these diuretics must be very carefully evaluated in patients with gout and diabetes.

- Very rare: hypercalcemia.

4.9 Overdosage

Indapamide has not shown any toxicity at doses of up to 40 mg, i.e. 27 times the therapeutic dose.

Above all, signs of acute poisoning take the form of water and electrolyte disturbances (hyponatremia and hypokalemia). Clinically, they include possible nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusional states, polyuria or oliguria up to the extent of anuria (due to hypovolemia).

Initial measures taken involve the rapid elimination of the product(s) ingested by gastric lavage and/or the administration of activated charcoal, followed by restoration of the fluid and the electrolyte balance to normal in a specialized center.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

DIURETIC ACTING AT THE CORTICAL DILUTION SEGMENT
ATC Code: CO3 BA 11 (Cardiovascular System)

Indapamide is a sulfonamide derivative with an indol ring, which is pharmacologically related to the thiazide diuretics, which act 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.

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.

Its antihypertensive activity 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-, medium- 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 the diabetic hypertensive patient.

5.2 Pharmacokinetic properties

NATRILIX SR is supplied in a sustained release dosage form based on a matrix system in which the active substance is dispersed in 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 speed of absorption but has no influence on the amount of drug absorbed.

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

Intra-individual variability exists.

Distribution
The binding of indapamide to plasma proteins is 79%;
The plasma elimination half-life is 14 to 24 hours (mean = 18 hours).
State of equilibrium is achieved after 7 days;
Repeated administration does not lead to accumulation.

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

Populations at-risk
Pharmacokinetic parameters are unchanged in renal failure patients.

5.3 Preclinical safety data

The highest doses administered in different animal species by the oral route (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of Indapamide. The main symptoms from acute toxicity studies with Indapamide administered by the intravenous or intraperitoneal route are related to the pharmacological activity of Indapamide, i.e. bradypnea and peripheral vasodilation.
Mutagenicity and carcinogenicity tests on Indapamide are negative.