SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Natrixam 1.5 mg / 5 mg modified-release tablets
Natrixam 1.5 mg / 10 mg modified-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 1.5 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.
One tablet contains 1.5 mg indapamide and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine.

Excipient with known effect: 104.5 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablet.
White, round, film-coated, bilayered, modified-release tablet of 9 mm diameter engraved with  on one face.
Pink, round, film-coated, bilayered, modified-release tablet of 9 mm diameter engraved with on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Natrixam is indicated as substitution therapy for treatment of essential hypertension in patients already controlled with indapamide and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration

Posology

One tablet per day as single dose, preferably to be taken in the morning, to be swallowed whole with water and not chewed.

The fixed dose combination is not suitable for initiation therapy.

If a change of the posology is required, titration should be done with the individual components.

Special populations

Paediatric population
The safety and efficacy of Natrixam in children and adolescents have not been established.
No data are available.

Patients with renal impairment (see sections 4.3 and 4.4):
In severe renal impairment (creatinine clearance below 30 ml/min), treatment is contraindicated.
In patients with mild to moderate renal impairment, no dose adjustment is needed.

Older people (see section 4.4 and 5.2):
Older people can be treated with Natrixam according to renal function.

Patients with hepatic impairment (see sections 4.3 and 4.4):

In severe hepatic impairment, treatment is contraindicated.
Dosage recommendations of amlodipine have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2).

Method of administration

Oral administration.

4.3 Contraindications

- hypersensitivity to the active substances, to other sulfonamides, to dihydropyridine derivatives or to any of the excipients listed in section 6.1
- severe renal failure (creatinine clearance below 30 ml/min)
- hepatic encephalopathy or severe impairment of liver function
- hypokalaemia
- lactation
- severe hypotension
- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis)
- haemodynamically unstable heart failure after acute myocardial infarction

4.4 Special warnings and precautions for use

Special warnings

Hepatic encephalopathy:
When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy, particularly in case of electrolyte imbalance. Due to the presence of indapamide, administration of Natrixam must be stopped immediately if this occurs.

Photosensitivity:
Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section 4.8). 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.

Precautions for use

Hypertensive crisis:
The safety and efficacy of amlodipine in hypertensive crisis have not been established.

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 4.8 and 4.9).
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. 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.

- 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:
Due to the presence of indapamide, monitoring of blood glucose is important in diabetics, in particular in the presence of hypokalaemia.

Cardiac failure:
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Renal function:
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.

Amlodipine may be used in patients with renal failure at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

The effect of the combination Natrixam has not been tested in renal dysfunction. In renal impairment, Natrixam doses should respect those of the individual components taken individually.

Uric acid:
Due to the presence of indapamide, tendency to gout attacks may be increased in hyperuricaemic patients.

Hepatic function:
The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose.

The effect of the combination Natrixam has not been tested in hepatic dysfunction. Taking into account the effect of indapamide and amlodipine, Natrixam is contra-indicated in patients with severe hepatic impairment, and caution should be exercised in patients with mild to moderate hepatic impairment.

Older people
Older patients can be treated with Natrixam according to renal function (see sections 4.2 and 5.2).

Excipients:
Natrixam should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Linked to indapamide:

Combinations that are not recommended:

Lithium:
Increased plasma lithium with signs of overdose, 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 medicines:
- 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 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 salicylic 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. 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.

Digitalis preparations:
Hypokalaemia predisposing to the toxic effects of digitalis.
Monitoring of plasma potassium and ECG and, if necessary, adjust the treatment.

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

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 increased (additive effect).

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

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

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

Linked to amlodipine:

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Ciclosporine: No drug interaction studies have been conducted with ciclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of ciclosporine were observed. Consideration should be given to monitoring ciclosporine levels in renal transplant patients on amlodipine, and ciclosporine dose reductions should be made as necessary.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

4.6 Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation:
Natrixam is not recommended during pregnancy.
Natrixam is contra-indicated during lactation.

Pregnancy

Linked to indapamide
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 foeto-placental ischaemia and growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported following exposure near term.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Linked to amlodipine
The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Breastfeeding

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

Linked to amlodipine
It is not known whether amlodipine is excreted in breast milk.

Fertility

Linked to indapamide
Reproductive toxicity studies showed no effect on fertility in female and male rats (see section 5.3). No effects on human fertility are anticipated.

Linked to amlodipine
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse reactions were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Natrixam has minor or moderate influence on the 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.
- Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions with indapamide and amlodipine given separately are hypokalaemia, somnolence, dizziness, headache, visual impairment, diplopia, palpitations, flushing, dyspnoea, abdominal pain, nausea, dyspepsia, change of bowel habit, diarrhoea, constipation, rash maculo-papular, ankle swelling, muscle spasms, oedema, fatigue and asthenia.

Tabulated list of adverse reactions
The following adverse reactions have been observed and reported during treatment with indapamide and amlodipine with the following frequencies: 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 (≤1/10,000); not known (cannot be estimated from the available data).

MedDRA System organ class	**Adverse reactions**	**Frequency**	
		Indapamide	**Amlodipine**
Infections and infestations	Rhinitis	-	Uncommon

Blood and lymphatic system disorders	Leukopenia	Very rare	Very rare
	Thrombocytopenia	Very rare	Very rare
	Agranulocytosis	Very rare	-
	Aplastic anaemia	Very rare	-
	Haemolytic anaemia	Very rare	-
Immune system disorders	Hypersensitivity	-	Very rare -
Metabolism and nutrition disorders	Hypokalaemia	Common During clinical studies, hypokalaemia (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. (see section 4.4).	-
	Hyperglycaemia	-	Very rare
	Hypercalcaemia	Very rare	-
	Hyponatraemia with hypovolaemia*	Not known	-
Psychiatric disorders	Insomnia	-	Uncommon
	Mood altered (including anxiety)	-	Uncommon
	Depression	-	Uncommon
	Confusional state	-	Rare
Nervous system disorders	Somnolence	-	Common (especially at the beginning of the treatment)
	Dizziness	-	Common (especially at the beginning of the treatment)
	Headache	Rare	Common (especially at the beginning of the treatment)
	Tremor	-	Uncommon
	Dysgeusia	-	Uncommon
	Syncope	Not known	Uncommon
	Hypoaesthesia	-	Uncommon
	Paraesthesia	Rare	Uncommon
	Hypertonia	-	Very rare
	Neuropathy peripheral	-	Very rare
	Extrapyramidal disorder (extrapyramidal syndrome)	-	Not known
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency	Not known (see sections 4.3 and 4.4)	-

Eye disorders	Visual impairment	Not known	Common
	Diplopia	-	Common
	Myopia	Not known	-
	Vision blurred	Not known	-
Ear and labyrinth disorders	Tinnitus	-	Uncommon
	Vertigo	Rare	-
Cardiac disorders	Palpitations	-	Common
	Myocardial infarction	-	Very rare
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	Uncommon
	Torsade de pointes (potentially fatal)	Not known (see sections 4.4 and 4.5)	-
Vascular disorders	Flushing		Common
	Hypotension	Very rare	Uncommon
	Vasculitis	-	Very rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	-	Common
	Cough	-	Uncommon
Gastrointestinal disorders	Abdominal pain	-	Common
	Nausea	Rare	Common
	Vomiting	Uncommon	Uncommon
	Dyspepsia	-	Common
	Change of bowel habit	-	Common
	Dry mouth	Rare	Uncommon
	Pancreatitis	Very rare	Very rare
	Gastritis	-	Very rare
	Gingival hyperplasia	-	Very rare
	Diarrhoea	-	Common
	Constipation	Rare	Common
Hepato-biliary disorders	Hepatitis	Not known	Very rare
	Jaundice	-	Very rare
	Hepatic function abnormal	Very rare	-
Skin and subcutaneous tissue disorders	Rash maculo-papular	Common	-
	Purpura	Uncommon	Uncommon
	Alopecia	-	Uncommon
	Skin discolouration	-	Uncommon
	Hyperhidrosis	-	Uncommon
	Pruritus	-	Uncommon
	Rash	-	Uncommon
	Exanthema	-	Uncommon
	Angioedema	Very rare	Very rare
	Urticaria	Very rare	Uncommon
	Toxic epidermal necrolysis	Very rare	-
	Stevens-Johnson syndrome	Very rare	Very rare
	Erythema multiforme	-	Very rare
	Exfoliative dermatitis	-	Very rare
	Quincke’s oedema	-	Very rare

	Photosensitivity	Cases of photosensitivity reactions have been reported (see section 4.4).	Very rare
Musculoskeletal and connective tissue disorders	Ankle swelling	-	Common
	Arthralgia	-	Uncommon
	Myalgia	-	Uncommon
	Muscle spasms	-	Common
	Back pain	-	Uncommon
	Possible worsening of pre-existing disseminated lupus erythematosus	Not known	-
Renal and urinary disorders	Micturition disorder	-	Uncommon
	Nocturia	-	Uncommon
	Pollakiuria	-	Uncommon
	Renal failure	Very rare	-
Reproductive system and breast disorders	Erectile dysfunction	-	Uncommon
	Gynaecomastia	-	Uncommon
General disorders and administration site conditions	Oedema	-	Very common
	Fatigue	Rare	Common
	Chest pain	-	Uncommon
	Asthenia	-	Common
	Pain	-	Uncommon
	Malaise	-	Uncommon
Investigations	Weight increased	-	Uncommon
	Weight decreased	-	Uncommon
	Electrocardiogram QT prolonged	Not known (see sections 4.4 and 4.5)	-
	Blood glucose increased	Not known Appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes	-
	Blood uric acid increased	Not known Appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes	-
	Hepatic enzyme increased	Not known	Very rare**

* responsible for 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.
** mostly consistent with cholestasis

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 the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with Natrixam in humans.

For indapamide:
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).

Treatment
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.

For amlodipine:
In humans experience with intentional overdose is limited.
Symptoms
Available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
Treatment
Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.
A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: calcic inhibitors and diuretics, ATC code: C08GA02

Mechanism of action

Indapamide is a sulfonamide 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.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle.

Pharmacodynamic effects

Phase II and III studies using indapamide 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.

In patients with hypertension, once daily dosing of amlodipine provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.
Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Clinical efficacy and safety

Natrixam has not been studied on morbidity and mortality.

In the case of amlodipine, a randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

Paediatric population
No data are available with Natrixam in children.
The European Medicines Agency has waived the obligation to submit the results of studies with Natrixam in all subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The co-administration of indapamide and amlodipine does not change their pharmacokinetic properties by comparison to separate administration.

Indapamide:
Indapamide 1.5 mg is supplied in a prolonged release dosage based on a matrix system in which the active 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 active substance 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.

Elimination:
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.

Amlodipine:
Amlodipine is supplied in an immediate release dosage.

Absorption, distribution, plasma protein binding:
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination
The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Use in older people
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

5.3 Preclinical safety data

Natrixam has not been studied in non clinical studies.

Indapamide:
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 or teratogenicity.
Fertility was not impaired either in male or female rats.

Amlodipine:

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Hypromellose (E464)
Lactose monohydrate
Magnesium stearate (E572)
Povidone (E1201)
Silica colloidal anhydrous
Calcium hydrogen phosphate dihydrate
Cellulose, microcrystalline (E460)
Croscarmellose sodium (E468)
Pregelatinized maize starch

Tablet film-coating:
Glycerol (E422)
Hypromellose (E464)

Macrogol 6000
Magnesium stearate (E572)
Titanium dioxide (E171)

Tablet core:
Hypromellose (E464)
Lactose monohydrate
Magnesium stearate (E572)
Povidone (E1201)
Silica colloidal anhydrous
Calcium hydrogen phosphate dihydrate
Cellulose, microcrystalline (E460)
Croscarmellose sodium (E468)
Pregelatinized maize starch

Tablet film-coating:
Glycerol (E422)
Hypromellose (E464)
Iron oxide red (E172)
Macrogol 6000
Magnesium stearate (E572)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Blisters (PVC/Aluminium): store below 30 °C
HDPE bottles: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blisters:
1x15 (15) tablets, 2x15 (30) tablets, 4x15 (60) tablets, 6x15 (90) tablets

High density polyethylene bottles equipped with a screw tamper evident polypropylene cap:
1x100 (100) tablets, 5x100 (500) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

For RMS (the Netherlands):

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex– France

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<[To be completed nationally]>

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON/CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Natrixam 1.5 mg / 5 mg modified-release tablets
indapamide / amlodipine

Natrixam 1.5 mg / 10 mg modified-release tablets
indapamide / amlodipine

2. STATEMENT OF ACTIVE SUBSTANCES

One tablet contains 1.5 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.
One tablet contains 1.5 mg indapamide and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 modified-release tablets
5 containers of 100 modified-release tablets

100 modified-release tablets
5 containers of 100 modified-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not chew or crush the tablets.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

For RMS (the Netherlands):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex– France

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Natrixam 1.5 mg / 5 mg
Natrixam 1.5 mg / 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON/BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Natrixam 1.5 mg / 5 mg modified-release tablets
indapamide / amlodipine

Natrixam 1.5 mg / 10 mg modified-release tablets
indapamide / amlodipine

2. STATEMENT OF ACTIVE SUBSTANCES

One tablet contains 1.5 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.
One tablet contains 1.5 mg indapamide and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

15 modified-release tablets
30 modified-release tablets
60 modified-release tablets
90 modified-release tablets

15 modified-release tablets
30 modified-release tablets
60 modified-release tablets
90 modified-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not chew or crush the tablets.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

For RMS (the Netherlands):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex– France

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Natrixam 1.5 mg / 5 mg
Natrixam 1.5 mg / 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Natrixam 1.5 mg / 5 mg modified-release tablets
indapamide / amlodipine
Natrixam 1.5 mg / 10 mg modified-release tablets
indapamide / amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

For RMS (the Netherlands):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex– France

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Batch {number}

5. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the patient

NATRIXAM 1.5 mg / 5 mg modified-release tablets
NATRIXAM 1.5 mg / 10 mg modified-release tablets

indapamide / amlodipine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Natrixam is and what it is used for

Natrixam is prescribed as substitution treatment for high blood pressure (hypertension) in patients already taking indapamide and amlodipine from separate tablets in the same strength.

Natrixam is a combination of two active ingredients, indapamide and amlodipine.
Indapamide is a diuretic. Diuretics increase the amount of urine produced by the kidneys. However, indapamide is different from other diuretics, as it only causes a slight increase in the amount of urine produced.
Amlodipine is a calcium antagonist (which belongs to a class of medicines called dihydropyridines) and it works by relaxing blood vessels, so that blood passes through them more easily. Each of the active ingredients reduces blood pressure.

2. What you need to know before you take Natrixam

Do not take Natrixam
- if you are allergic to indapamide or any other sulfonamide (class of medicinal product for the treatment of hypertension), or to amlodipine or any other calcium antagonist (class of medicinal produt for the treatment of hypertension) or to any of the other ingredients of this medicine (listed in section 6)). This may be itching, reddening of the skin or difficulty in breathing,
- if you have severe low blood pressure (hypotension),
- if you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body),
- if you suffer from heart failure after a heart attack,
- if you have severe kidney disease,
- if you have severe liver disease or suffer from a condition called hepatic encephalopathy (disease of the brain caused by liver illness),
- if you have low potassium levels in your blood,
- if you are breastfeeding.

Warnings and precautions
Talk to your doctor or pharmacist before taking Natrixam.

You should inform your doctor if you have or have had any of the following conditions:
- recent heart attack,
- if you have heart failure, any heart rhythm problems, if you have coronary artery disease (heart disease caused by poor blood flow in the blood vessels of the heart),
- if you have problems with your kidneys,
- severe increase in blood pressure (hypertensive crisis),
- you are elderly and your dose needs to be increased,
- if you take other medicines,
- if you are malnourished,
- if you have liver problems,
- if you have diabetes,
- if you suffer from gout,
- if you need to have a test to check how well your parathyroid gland is working,
- if you have had photosensitivity reactions.

Your doctor may prescribe you blood tests to check for low sodium or potassium levels or high calcium levels. If you think any of these situations may apply to you or you have any questions or doubts about taking your medicine, you should consult your doctor or pharmacist.

Children and adolescents
Natrixam should not be given to children and adolescents.

Other medicines and Natrixam
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take Natrixam:
- with lithium (used to treat mental disorders such as mania, manic depressive illness and recurrent depression) due to the risk of increased levels of lithium in the blood,
- with dantrolene (infusion for severe body temperature abnormalities).

Make sure to tell your doctor if you are taking any of the following medicines, as special care may be required:
- other medicines for treating high blood pressure,
- medicines used for heart rhythm problems (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, ibutilide, dofetilide),
- medicines used to treat mental disorders such as depression, anxiety, schizophrenia… (e.g. tricyclic antidepressants, antipsychotic drugs, neuroleptics),
- bepridil (used to treat angina pectoris, a condition causing chest pain),
- cisapride, diphemanil (used to treat gastro-intestinal problems),
- sparfloxacin, moxifloxacin, erythromycin by injection (antibiotics used to treat infections),
- vincamine IV (used to treat symptomatic cognitive disorders in elderly including memory loss),
- halofantrine (antiparasitic drug used to treat certain types of malaria),
- pentamidine (used to treat certain types of pneumonia),
- mizolastine (used to treat allergic reactions, such as hay fever),
- non-steroidal anti-inflammatory drugs for pain relief (e.g. ibuprofen) or high doses of acetylsalicylic acid,
- angiotensin converting enzyme (ACE) inhibitors (used to treat high blood pressure and heart failure),
- oral corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis,
- digitalis preparations (for the treatment of heart problems),
- stimulant laxatives,
- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis),
- potassium-sparing diuretics (amiloride, spironolactone, triamterene),
- metformin (to treat diabetes),
- iodinated contrast media (used for tests involving X-rays),
- calcium tablets or other calcium supplements,

- immunosuppressants (medicines which reduce the defense mechanism of the body) used for the treatment of auto-immune disorders of following transplant surgery (e.g. ciclosporine, tacrolimus),
- tetracosactide (to treat Crohn's disease),
- ketoconazole, itraconazole, amphotericin B by injection (anti-fungal medicines),
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV),
- rifampicin, erythromycin, clarithromycin (antibiotics for infection caused by bacteria),
- hypericum perforatum (St. John's Wort),
- verapamil, diltiazem (heart medicines),
- simvastatin (cholesterol lowering medicine) ,
- allopurinol (to treat gout).

Natrixam with food and drink
Grapefruit juice and grapefruit should not be consumed by people who are taking Natrixam. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Natrixam.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
This medicine is not recommended during pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible.

You must not take Natrixam if you are breast-feeding. Tell your doctor immediately if you are breast-feeding or about to start breast-feeding.

Driving and using machines
Natrixam may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately. If this occurs, you should refrain from driving and other activities requiring alertness.

Natrixam contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Natrixam

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet once a day, preferably in the morning.
The tablet should be swallowed whole with water and should not be chewed.

If you take more Natrixam than you should
Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, drowsy, lightheaded, faint or weak. You may experience nausea, vomiting, cramps, confusion and changes in the amount of urine produced by the kidneys. If a blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many Natrixam tablets.

If you forget to take Natrixam
Do not worry. If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Natrixam
As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping this medicinal product.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking the medicinal product and visit your doctor immediately if you experience any of the following side effects:
- swelling of eyelids, face or lips (very rare, may affect up to 1 in 10,000 people),
- swelling of the tongue and throat which causes great difficulty breathing (very rare, may affect up to 1 in 10,000 people),
- severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome) or other allergic reactions (very rare, may affect up to 1 in 10,000 people),
- heart attack (very rare, may affect up to 1 in 10,000 people),
- abnormal heart beat (uncommon, may affect up to 1 in 100 people),
- life-threatening irregular beat (torsade de pointes) (frequency not known),
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell (very rare, may affect up to 1 in 10,000 people).

The following common side-effects have been reported. If any of these cause you problems or if they last for more than one week, you should contact your doctor.

Very common: may affect more than 1 in 10 people
- oedema (fluid retention).

Common: may affect up to 1 in 10 people
- headache, dizziness, sleepiness (especially at the beginning of treatment),
- visual impairment, double vision,
- palpitations (awareness of your heart beat), flushing,
- shortness of breath,
- abdominal pain, feeling sick (nausea), change of bowel habit, diarrhoea, constipation, indigestion,
- ankle swelling, tiredness, weakness, muscle spasms,
- low potassium in the blood, which may cause muscle weakness,
- skin rashes.

Other side effects that have been reported include the following list. If any of these get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Uncommon: may affect up to 1 in 100 people
- mood altered, anxiety, depression, sleeplessness,
- trembling,
- taste abnormalities,
- numbness or tingling sensation in your limbs, loss of pain sensation,
- ringing in the ears,
- low blood pressure,
- fainting,
- sneezing/running nose caused by inflammation of the lining of the nose (rhinitis),
- cough,dry mouth, vomiting (being sick),
- hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration, hives,
- disorder in passing urine, increased need to urinate at night, increased number of times of passing urine,
- inability to obtain an erection; discomfort or enlargement of the breasts in men,
- pain, feeling unwell,
- joint or muscle pain, back pain,
- weight increased or decreased.

Rare: may affect up to 1 in 1,000 people
- confusional state,
- feeling of dizziness.

Very rare: may affect up to 1 in 10,000 people
- changes in blood cells, such as thrombocytopenia (decrease in the number of platelets which causes easy bruising and nasal bleeding), leucopenia (decrease of white blood cells which may cause unexplained fever, soreness of the throat or other flu-like symptoms – if this occurs, contact your doctor) and anaemia (decrease in red blood cells),
- excess sugar in blood (hyperglycaemia),
- increase of calcium in blood,
- a disorder of the nerves which can cause weakness, tingling or numbness,
- swelling of the gums,
- abdominal bloating (gastritis),
- hepatic function abnormal, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests ; in cases of liver failure, there is a possibility of getting hepatic encephalopathy (disease in the brain caused by liver illness),
- kidney disease,
- increased muscle tension,
- inflammation of blood vessels, often with skin rash,
- sensitivity to light.

Not known (frequency cannot be estimated from the available data):
- changes may occur in your laboratory parameters and your doctor may need to give you blood tests to check your condition. The following changes in laboratory parameters may occur:
  . low sodium in the blood that may lead to dehydration and low blood pressure,
  . increase in uric acid, a substance which may cause or worsen gout (painful joint(s) especially in the feet),
  . increase in blood glucose levels in diabetic patients,
- abnormal ECG tracing,
- short sightedness (myopia).
- vision blurred.
- trembling, rigid posture, mask-like face, slow movements and a shuffling, unbalanced walk.

If you suffer from systemic lupus erythematosus (a type of collagen disease), this might get worse.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.
You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Natrixam

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister or container. The expiry date refers to the last day of that month.

Blisters: store below 30°C.
Bottles: this medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Natrixam contains

- The active substances are indapamide and amlodipine.
  One tablet of Natrixam 1.5 mg / 5 mg contains 1.5 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.
  One tablet of Natrixam 1.5 mg / 10 mg contains 1.5 mg indapamide and 13.87 mg amlodipine besilate equivalent to 10 mg amlodipine.
- The other ingredients are:
  - Tablet core for Natrixam 1.5mg/5mg and 1.5mg/10mg: lactose monohydrate, hypromellose (E464), magnesium stearate (E572), povidone (E1201), silica colloidal anhydrous, calcium hydrogen phosphate dihydrate, cellulose microcrystalline (E460), croscarmellose sodium (E468), pregelatinised maize starch,
  - Tablet film-coating for Natrixam 1.5mg/5mg: glycerol (E422), hypromellose (E464), macrogol 6000, magnesium stearate (E572), titanium dioxide (E171),
  - Tablet film-coating for Natrixam 1.5mg/10mg: glycerol (E422), hypromellose (E464), iron oxide red (E172), macrogol 6000, magnesium stearate (E572), titanium dioxide (E171).

What Natrixam looks like and contents of the pack
Natrixam 1.5 mg / 5 mg tablets are white, round, film-coated, modified-release tablets of 9 mm diameter engraved with  on one face.
Natrixam 1.5 mg /10 mg tablets are pink, round, film-coated, modified-release tablets of 9 mm diameter engraved with on one face.

The tablets are available in blisters of 15, 30, 60, 90 tablets and containers of 100 and 500 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
<[To be completed nationally]>

For RMS (the Netherlands):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex– France

Manufacturers
Les Laboratoires Servier Industrie
905 route de Saran
45520 Gidy - France

and

Servier (Ireland) Industries Ltd (SII)
Moneylands, Gorey Road
Arklow – Co. Wicklow – Ireland

and

Anpharm Przedsiebiorstwo Farmaceutyczne S.A.

03-236 Warszawa
ul. Annopol 6b – Poland

and

Laboratorios Servier S.L.
Avenida de los Madronos, 33
28043 Madrid - Spain

and

Egis Pharmaceuticals PLC
H-1165 Budapest,
Bökényföldi út 118-120,
Hungary

and

Egis Pharmaceuticals PLC
H- 9900 Körmend ,
Mátyás király u. 65,
Hungary

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	NATRIXAM®, Tabletten mit veränderter Wirkstofffreisetzung
Belgium	NADREXAM® comprimé à libération modifiée
Bulgaria	NATRIXAM®, таблетки с изменено освобождаване
Croatia	NATRIXAM® tablete s prilagođenim oslobađanjem
Cyprus	NATRIXAM®, δισκία ελεγχόμενης αποδέσμευσης
Czech Republic	NATRIXAM®, tablety s řízeným uvolňováním
Estonia	NATRIXAM®
Finland	NATRIXAM®, depottabletti
France	NATRIXAM®, comprimé à libération modifiée
Germany	NATRIXAM®, Tabletten mit veränderter Wirkstofffreisetzung
Greece	NATRIXAM®, δισκία ελεγχόμενης αποδέσμευσης
Hungary	NATRIXAM® módosított hatóanyagleadású tabletta
Italy	NATRILOR®, compresse a rilascio modificato
Latvia	TERTENSAM®, ilgstošās darbības tabletes
Lithuania	NATRIXAM®, modifikuoto atpalaidavimo tabletės
Luxembourg	NADREXAM®, comprimé à libération modifiée
Malta	NATRIXAM®, modified-release tablets
Netherlands	NATRIXAM®, tabletten met gereguleerde afgifte
Poland	TERTENS-AM®
Portugal	NATRIXAM®, comprimidos de libertação modificada
Romania	NATRIXAM® comprimate cu eliberare modificată
Slovakia	NATRIXAM®, tablety s riadeným uvoľňovaním
Slovenia	NADEXAM® tablete s prirejenim sproščanjem
Spain	NATRIXAM® comprimidos de liberación modificada

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

<[To be completed nationally]>

<Other sources of information>

<Detailed information on this medicine is available on the web site of {MA/Agency}>