

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.

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 sulphonamides, 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. Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. 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).

• 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 (see section 5.1). 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 μ mol/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 contraindicated 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.

Combinations to be taken into consideration:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene):

Whilst rational combinations are useful in some patients, hypokalaemia (particularly in patients with renal failure or diabetes) or hyperkalaemia 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 $\mu\text{mol/l}$) in men and 12 mg/l (110 $\mu\text{mol/l}$) 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.

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).

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.

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, warfarin or ciclosporin.

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

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 hypoglycemia and thrombocytopenia in neonates have been reported following

exposure near term.

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

Indapamide is excreted in human milk. Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of milk lactation. Hypersensitivity to sulphonamide-derived medicines and hypokalaemia might occur.

Linked to amlodipine

It is not known whether amlodipine is excreted

in breast milk. Fertility

Linked to indapamide

Indapamide has no effect on reproductive performance or fertility.

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 somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare

($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$); not known (cannot be estimated from the available data).

| MedDRA System organ class | Adverse reactions | Frequency | |
|---|----------------------------------|--|---|
| | | Indapamide | Amlodipine |
| Blood and lymphatic system disorders | Leukocytopenia | Very rare | Very rare |
| | Thrombocytopenia | Very rare | Very rare |
| | Agranulocytosis | Very rare | - |
| | Aplastic anaemia | Very rare | - |
| | Haemolytic anaemia | Very rare | - |
| Immune system disorders | Allergic reactions | - | 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 | Not known | - |
| | h hypovolaemia* | | |
| Psychiatric disorders | Insomnia | - | Uncommon |
| | Mood changes (including anxiety) | - | Uncommon |
| | Depression | - | Uncommon |
| | Confusion | - | 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 |
| | Hypoesthesia | - | Uncommon |
| | Paresthesia | Rare | Uncommon |
| | Vertigo | Rare | - |
| | Hypertonia | - | Very rare |
| | Peripheral neuropathy | - | Very rare |
| Eye disorders | Visual disturbance (including diplopia) | - | Uncommon |
| Ear and labyrinth disorders | Tinnitus | - | Uncommon |
| Cardiac disorders | Palpitations | - | Common |
| | Myocardial infarction | - | Very rare |
| | Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) | Very rare | Very rare |
| | 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 | - | Uncommon |
| | Rhinitis | - | Uncommon |
| | Cough | - | Very rare |
| Gastrointestinal disorders | Abdominal pain | - | Common |
| | Nausea | Rare | Common |
| | Vomiting | Uncommon | Uncommon |
| | Dyspepsia | - | Uncommon |
| | Altered bowel habits (including diarrhoea and constipation) | - | Uncommon |
| | Dry mouth | Rare | Uncommon |
| | Pancreatitis | Very rare | Very rare |
| | Gastritis | - | Very rare |
| | Gingival hyperplasia | - | Very rare |
| Constipation | Rare | Uncommon | |
| | Hepatitis | Not known | Very rare |

| | | | |
|---|---|--------------------------------------|-------------|
| Hepato-biliary disorders | Jaundice | - | Very rare |
| | Hepatic enzymes increased | Not known | Very rare** |
| | Abnormal hepatic function | Very rare | - |
| | Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency | Not known (see sections 4.3 and 4.4) | - |
| Skin and subcutaneous tissue disorders | Maculopapular rashes | 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 | Very rare |
| | Toxic epidermal necrolysis | Very rare | - |
| | Steven Johnson syndrome | Very rare | Very rare |
| | Erythema multiforme | - | Very rare |
| | Exfoliative dermatitis | - | Very rare |
| | Quincke oedema | - | Very rare |
| Photosensitivity | Cases of photosensitivity reactions have been reported (see section 4.4). | Very rare | |
| Possible worsening of pre-existing acute disseminated lupus erythematosus | Not known | - | |
| Musculoskeletal and connective tissue disorders | Ankle swelling | - | Common |
| | Arthralgia | - | Uncommon |
| | Myalgia | - | Uncommon |
| | Muscle cramps | - | Uncommon |
| | Back pain | - | Uncommon |
| Renal and urinary disorders | Micturition disorder | - | Uncommon |
| | Nocturia | - | Uncommon |
| | Increased urinary frequency | - | Uncommon |

| | | | |
|---|--------------------------------|--------------------------------------|----------|
| | Renal failure | Very rare | - |
| Reproductive system and breast disorders | Impotence | - | Uncommon |
| | Gynaecomastia | - | Uncommon |
| General disorders and administration site conditions | Oedema | - | Common |
| | Fatigue | Rare | Common |
| | Chest pain | - | Uncommon |
| | Asthenia | - | Uncommon |
| | Pain | - | Uncommon |
| | Malaise | - | Uncommon |
| Investigations | Weight increase | - | Uncommon |
| | Weight decrease | - | Uncommon |
| | Electrocardiogram QT prolonged | Not known (see sections 4.4 and 4.5) | - |

| | | | |
|--|--|--|---|
| | Blood glucose increased and blood uric acid increased during treatment | Not known Appropriateness of these diuretics must be very carefully weighed in patients with gout or diabetes | - |
|--|--|--|---|

* 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

Exceptional cases of extrapyramidal syndrome have been reported with amlodipine. 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:

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).

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 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.

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:

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. Indapamide has been tested negative concerning mutagenic and carcinogenic properties. 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

24 months

6.4 Special precautions for storage

Store below 30 °C

6.5 Nature and contents of container

Blisters in Aluminium/ Polyamide-Aluminium-polyvinyl choride complex, 5, 10, 15, 30, 60 and 90 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
LES LABORATOIRES SERVIER

10. DATE OF REVISION OF THE TEXT
September 2013