INDAPAMIDE + AMLODIPINE

NATRIXAM 1.5 mg/5 mg

NATRIXAM 1.5 mg/10 mg

Modified-release Tablet
Antihypertensive
(Diuretic/Calcium Channel Blocker)

DESCRIPTION:

Natrixam 1.5 mg/5 mg: White, round, film-coated, bilayered, modified-release tablet of 9 mm diameter engraved with * on one face. Natrixam 1.5 mg/10 mg: Pink, round, film-coated, bilayered, modified-release tablet of 9 mm diameter engraved with * on one face.

FORMULATION:

Natrixam 1.5 mg/5 mg: One modified-release tablet contains 1.5 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.
Natrixam 1.5 mg/10 mg: One modified-release 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.

PHARMACODYNAMICS AND PHARMACOKINETICS:

Pharmacodynamics:

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.

Pharmacokinetics:

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 fecal (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 metabolized 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.

INDICATION:

Indapamide + Amlodipine (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.

DOSAGE AND ADMINISTRATION:

Oral use.
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 as whole with water and should not be chewed.

GENERAL INFORMATIONS			NUMBER PAGES
PIL_FT_K_#03 160 x 210 mm (88)_NATRIXAM 1.5/5 MG_LGS_001 28/08/2023 3336_11.02 PHILIPPINES (PHL)	Font size: 8 pts Line spacing: 8 pts Font size of the section headings: 10 pts Font type: Helvetica Neue LT Pro	**SPOTS COLORS** BLACK	6 pages

CONTRAINDICATIONS:

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

WARNINGS AND PRECAUTIONS:

Special warnings

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

Photosensitivity: Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. 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.
  Any diuretic treatment may cause hyponatremia, sometimes with very serious consequences. Hyponatremia with hypovolemia 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 hypokalemia is the major risk of thiazide and related diuretics. Hypokalemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalemia. The risk of onset of hypokalemia (<3.4 mmol/l) must be prevented in certain high risk populations, *i.e.* the elderly, malnourished and/or polymedicated, cirrhotic patients with edema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal 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 hypokalemia requires its correction. Hypokalemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

- Plasma magnesium: Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.
- Plasma calcium: Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcemia may be due to previously unrecognized 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 hypokalemia.

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 edema 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.

Hypovolemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in 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 dialyzable.

The effect of the combination Indapamide + Amlodipine (Natrixam) has not been tested in renal dysfunction. In renal impairment, Indapamide + Amlodipine (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 hyperuricemic 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 Indapamide + Amlodipine (Natrixam) has not been tested in hepatic dysfunction. Taking into account the effect of indapamide and amlodipine, Indapamide + Amlodipine (Natrixam) is contraindicated in patients with severe hepatic impairment, and caution should be exercised in patients with mild to moderate hepatic impairment.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma: Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Athletes: Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

Older people: Older patients can be treated with Indapamide + Amlodipine (Natrixam) according to renal function.

Excipients: Indapamide + Amlodipine (Natrixam) should not be administered to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Level of sodium: Indapamide + Amlodipine (Natrixam) contains less than 1 mmol sodium (23 mg) per tablet, *i.e.* essentially 'sodium-free'.

PREGNANCY AND LACTATION:

Given the effects of the individual components in this combination product on pregnancy and lactation:
Indapamide + Amlodipine (Natrixam) is not recommended during pregnancy.
Indapamide + Amlodipine (Natrixam) is not recommended 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 feto-placental ischemia and growth retardation. Moreover, rare cases of hypoglycemia 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.

Linked to amlodipine: The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding

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

Linked to amlodipine: Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Fertility

Linked to indapamide: Reproductive toxicity studies showed no effect on fertility in female and male rats. 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.

DRIVING AND USING MACHINES:

Indapamide + Amlodipine (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.

INTERACTIONS:

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 such as but not limited to:

- class Ia antiarrhythmic agents (*e.g.* quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmic agents (*e.g.* amiodarone, sotalol, dofetilide, ibutilide, bretylium),
- some antipsychotics: phenothiazines (*e.g.* chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (*e.g.* amisulpride, sulpiride, sultopride, tiapride), butyrophenones (e.g. droperidol, haloperidol), other antipsychotic (*e.g.* pimozide),
- other substances: (*e.g.* bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV, methadone, astemizole, terfenadine).

Increased risk of ventricular arrhythmias, particularly *torsades de pointes* (hypokalemia is a risk factor).

Monitor for hypokalemia 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 hypokalemia.

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

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

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

- either to stop the diuretic 3 days before starting treatment with the A.C.E. inhibitor, and restart a hypokalemic 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 hypokalemic diuretic.
In all cases, monitor renal function (plasma creatinine) during the first weeks of treatment with an A.C.E. inhibitor.

Other compounds causing hypokalemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives: Increased risk of hypokalemia (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: Hypokalemia and/or hypomagnesaemia predispose to the toxic effects of digitalis.
Monitoring of plasma potassium, magnesium 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, hypokalemia or hyperkalemia (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 hypercalcemia resulting from decreased urinary elimination of calcium.

Ciclosporine, 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 hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, 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: Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (*e.g.* rifampicin, *hypericum perforatum*).

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.

Mechanistic Target of Rapamycin (mTOR) Inhibitors: mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

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.

ADVERSE DRUG REACTIONS:

Summary of the safety profile

The most commonly reported adverse reactions with indapamide and amlodipine given separately are hypokalemia, somnolence, dizziness, headache, visual impairment, diplopia, palpitations, flushing, dyspnea, abdominal pain, nausea, dyspepsia, change of bowel habit, diarrhea, constipation, rash maculo-papular, ankle swelling, muscle spasms, edema, 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 anemia	Very rare	-
	Hemolytic anemia	Very rare	-
Immune system disorders	Hypersensitivity	-	Very rare
Metabolism and nutrition disorders	Hypokalemia	Common	-
	Hyponatremia with hypovolemia*	Uncommon	-
	Hypochloraemia	Rare	-
	Hypomagnesaemia	Rare	-
	Hyperglycemia	-	Very rare
	Hypercalcemia	Very rare	-
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)

MedDRA System organ class	Adverse reactions	Frequency	
		Indapamide	Amlodipine
Nervous system disorders	Tremor	-	Uncommon
	Dysgeusia	-	Uncommon
	Syncope	Not known	Uncommon
	Hypoesthesia	-	Uncommon
	Paresthesia	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	-
Eye disorders	Visual impairment	Not known	Common
	Diplopia	-	Common
	Myopia	Not known	-
	Acute angle-closure glaucoma	Not known	
	Choroidal effusion	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	-
Vascular disorders	Flushing		Common
	Hypotension	Very rare	Uncommon
	Vasculitis	-	Very rare
Respiratory, thoracic and mediastinal disorders	Dyspnea	-	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
	Diarrhea	-	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

MedDRA System organ class	Adverse reactions	Frequency	
		Indapamide	Amlodipine
Skin and subcutaneous tissue disorders	Skin discoloration	-	Uncommon
	Hyperhidrosis	-	Uncommon
	Pruritus	-	Uncommon
	Rash	-	Uncommon
	Exanthema	-	Uncommon
	Angioedema	Very rare	Very rare
	Urticaria	Very rare	Uncommon
	Toxic epidermal necrolysis	Very rare	Not known
	Stevens-Johnson syndrome	Very rare	Very rare
	Erythema multiforme	-	Very rare
	Exfoliative dermatitis	-	Very rare
	Quincke's edema	-	Very rare
	Photosensitivity	Cases of photo-sensitivity reactions have been reported	Very rare
Musculoskeletal and connective tissue disorders	Ankle swelling	-	Common
	Arthralgia	-	Uncommon
	Myalgia	Not known	Uncommon
	Muscle spasms	Not known	Common
	Muscular weakness	Not known	
	Rhabdomyolysis	Not known	
	Back pain	-	Uncommon
	Possible worsening of pre-existing systemic 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	Uncommon
	Gynecomastia	-	Uncommon
General disorders and administration site conditions	Edema	-	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	-
	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

Description of selected adverse reactions
During phase II and III studies comparing indapamide 1.5mg and 2.5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- Indapamide 1.5 mg: 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.
- Indapamide 2.5 mg: Plasma potassium <3.4 mmol/l was seen in 25% of patients and <3.2 mmol/l in 10% of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

REPORTING OF ADVERSE DRUG REACTION:
For suspected adverse drug reaction, report to the FDA at ***www.fda.gov.ph***
Seek medical attention immediately at the first sign of any adverse drug reaction.

OVERDOSE AND TREATMENT:
There is no information on overdose with Indapamide + Amlodipine (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 (hyponatremia, hypokalemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolemia).
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 specialized center.

For amlodipine:
In humans, experience with intentional overdose is limited.
Symptoms: Available data suggest that gross overdose could result in excessive peripheral vasodilation 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.

MISSED DOSE:
If a dose is forgotten, leave out that dose completely. Take the next dose at the right time. Do not take a double dose to make up for a forgotten dose.

DISCONTINUATION OF TREATMENT:
As the treatment for high blood pressure is usually life-long, patient should discuss with the doctor before stopping this medicinal product.
If patient has any further questions on the use of this medicine, ask the doctor or pharmacist.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.
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. The expiry date refers to the last day of that month.
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.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

PACKAGING:
Natrixam 1.5 mg/5 mg: Alu/Alu Blister Pack x 5's (Box of 30's).
Natrixam 1.5 mg/10 mg: Alu/Alu Blister Pack x 5's (Box of 30's).

SERVIER

Les Laboratoires Servier – France
Manufactured by:
Les Laboratoires Servier Industrie
905 route de Saran,
45520 Gidy, France

Imported by:
SERVIER PHILIPPINES, INC.
Unit AD, 11F, 8 Rockwell, Hidalgo Drive,
Rockwell Center, Brgy. Poblacion,
Makati, Metro Manila

Distributed by:
Zuellig Pharma Corporation
Km. 14 West Service Road,
South Super Highway cor. Edison Ave.
Sun Valley, Parañaque City

Reg. Nos.: DR-XY44704; DR-XY44705
Date of First Authorization: 7 July 2015
Date of Revision of Package Insert: 07 July 2023