PERINDOPRIL ARGININE + INDAPAMIDE + AMLODIPINE

TRIPLIXAM®

5mg/1.25mg/5mg Film-coated tablet
5mg/1.25mg/10mg Film-coated tablet
10mg/2.5mg/10mg Film-coated tablet

ANTIHYPERTENSIVE

DESCRIPTION:

Triplixam 5mg/1.25mg/5mg: white, oblong, film-coated tablet, 9.75 mm long and 5.16 mm wide, engraved with "5" on one face and "5" on the other face.

Triplixam 5mg/1.25mg/10mg: white, oblong, film-coated tablet, 10.7 mm long and 5.66 mm wide, engraved with "5" on one face and "10" on the other face.

Triplixam 10mg/2.5mg/10mg: white, oblong, film-coated tablet, 12.2 mm long and 6.46 mm wide, engraved with "10" on one face and "10" on the other face.

FORMULATION:

- One film-coated tablet of Triplixam 5mg/1.25mg/5mg contains 3.395mg perindopril equivalent to 5mg perindopril arginine, 1.25mg indapamide, EP and 6.935mg amlodipine besilate, EP equivalent to 5mg of amlodipine.
- One film-coated tablet of Triplixam 5mg/1.25mg/10mg contains 3.395mg perindopril equivalent to 5mg perindopril arginine, 1.25mg indapamide, EP and 13.870mg amlodipine besilate, EP equivalent to 10mg of amlodipine.
- One film-coated tablet of Triplixam 10mg/2.5mg/10mg contains 6.790mg perindopril equivalent to 10mg perindopril arginine, 2.5mg indapamide, EP and 13.870mg amlodipine besilate, EP equivalent to 10mg of amlodipine.

PHARMACODYNAMICS AND PHARMACOKINETICS:

Pharmacodynamics

Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is a combination of three antihypertensive components with complementary mechanisms to control blood pressure in patient with hypertension. Perindopril arginine salt is an angiotensin converting enzyme inhibitor, indapamide, a chlorosulphamoyl diuretic and amlodipine, a calcium ion flux inhibitor of the dihydropyridine group.
The pharmacological properties of Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** are derived from those of each of the components taken separately. In addition, the combination of perindopril / indapamide produces an additive synergy of the antihypertensive effects of the two components.

Mechanism of action

Perindopril:

Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.

This results in:

- a reduction in aldosterone secretion,
- an increase in plasma renin activity, since aldosterone no longer exercises negative feedback,
- a reduction in total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney, with no accompanying salt and water retention or reflex tachycardia, with chronic treatment.

The antihypertensive action of perindopril also occurs in patients with low or normal renin concentrations.
Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Perindopril reduces the work of the heart:

- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins: reduction in pre-load,
- by reduction of the total peripheral resistance: reduction in afterload.

Studies carried out on patients with cardiac insufficiency have shown:

- a reduction in left and right ventricular filling pressures,
- a reduction in total peripheral vascular resistance,
- an increase in cardiac output and an improvement in the cardiac index,
- an increase in regional blood flow in muscle.

Exercise test results also showed improvement.

Indapamide:

Indapamide is a sulfonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits 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:

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.

Pharmacodynamic effects

Perindopril / indapamide:

In hypertensive patients regardless of age, the perindopril / indapamide combination exerts a dose-dependent anti-hypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

Perindopril:

Perindopril is active in all grades of hypertension: mild to moderate or severe. A reduction in systolic and diastolic arterial pressure is observed in the lying and standing position. The antihypertensive activity after a single dose is maximal at between 4 and 6 hours and is maintained over 24 hours. There is a high degree of residual blocking of angiotensin converting enzyme at 24 hours, approximately 80%.
In patients who respond, normalised blood pressure is reached after one month and is maintained without tachyphylaxis. Withdrawal of treatment has no rebound effect on hypertension.
Perindopril has vasodilatory properties and restores elasticity of the main arterial trunks, corrects histomorphometric changes in resistance arteries and produces a reduction in left ventricular hypertrophy.
If necessary, the addition of a thiazide diuretic leads to an additive synergy.
The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

Indapamide:

Indapamide, as monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal.
Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance.
Indapamide reduces left ventricular hypertrophy.
When a dose of thiazide diuretic and thiazide-related diuretics is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the dose should not be increased.

Furthermore, it has been shown that in the short-term, mid-term and long-term in hypertensive patients, indapamide:

- has no effect on lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol,
- has no effect on carbohydrate metabolism, even in diabetic hypertensive patients.

Amlodipine:

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions:
Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).
In patients with hypertension, once daily dosing 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.

Pharmacokinetic

Perindopril arginine + Indapamide + Amlodipine (TRIPLIXAM):

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

Perindopril:

Absorption and bioavailability: After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour (perindopril is a prodrug and perindoprilat the active metabolite). The plasma half-life of perindopril is equal to 1 hour. As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.
Distribution: The volume of distribution is approximately 0.2 L/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.
Biotransformation: Perindopril is a prodrug. Twenty-seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.
Elimination: Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.
Linearity / non-linearity: It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Special Populations:

- *Elderly:* Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure.
- *Renal impairment:* Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).
- *In case of dialysis:* clearance of perindoprilat is equal to 70 mL/min.
- *In patients with cirrhosis:* Perindopril pharmacokinetics is modified; hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required.

Indapamide:

Absorption: Indapamide is rapidly and completely absorbed from the digestive tract.
The peak plasma level is reached in humans approximately one hour after oral administration of the product.
Distribution: Plasma protein binding is 79%.
Metabolism and Elimination: The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation.
Elimination is mainly in the urine (70% of the dose) and feces (22%) in the form of inactive metabolites.
Special populations:
The pharmacokinetics is unchanged in patients with renal insufficiency.

Amlodipine:

Absorption and Bioavailability: 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 bioavailability of amlodipine is not affected by food intake.
Distribution: 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.
Metabolism: Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Elimination: The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Special populations:

- Use in the elderly: 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.
- Use in patients with impaired hepatic function: 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%.

INDICATION:

Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is indicated as substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril / indapamide fixed dose combination and amlodipine, taken at the same dose level.

DOSAGE AND ADMINISTRATION:

Posology

One Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** film-coated tablet per day as a single dose, preferably to be taken in the morning and before a meal.

The fixed dose combination is not suitable for initial therapy.

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

Special population

- *Renal impairment:* In severe renal impairment (creatinine clearance below 30 mL/min), treatment is contraindicated. In patients with moderate renal impairment (creatinine clearance 30-60 mL/min), Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** at the dose 10mg/2.5mg/10mg is contraindicated. It is recommended to start treatment with the adequate dosage of the free combination.
  Usual medical follow-up will include frequent monitoring of creatinine and potassium.
  Concomitant use of perindopril with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1.73 m²).
- *Hepatic impairment:* In severe hepatic impairment, Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is contraindicated.
  In patients with mild to moderate hepatic impairment, Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** should be administrated with caution, as dosage recommendations for amlodipine in these patients have not been established.
- *Elderly:* Elimination of perindoprilat is decreased in the elderly.
  Elderly can be treated with Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** according to renal function.
- *Pediatric population:* The safety and efficacy of Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** in children and adolescents have not been established. No data are available.

Method of administration

Oral use.

CONTRAINDICATIONS:

- Dialysis patients
- Patients with untreated decompensated heart failure
- Severe renal impairment (creatinine clearance below 30 mL/min)
- Moderate renal impairment (creatinine clearance below 60 mL/min) for Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** doses containing 10mg/2.5mg of perindopril / indapamide combination (*i.e.*, Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** 10mg/2.5mg/10mg)
- Hypersensitivity to the active substances, to other sulfonamides, to dihydropyridine derivatives, any other ACE-inhibitor or to any of the excipients.
- History of angioedema (Quincke's edema) associated with previous ACE inhibitor therapy
- Hereditary / idiopathic angioedema
- Second and third trimesters of pregnancy
- Hepatic encephalopathy
- Severe hepatic impairment
- 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
- Concomitant use of Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60mL/min/1.73m²)
  - Concomitant use with sacubitril / valsartan. Triplixam must not be initiated earlier than 36 hours after the last dose of sacubitril / valsartan
  - Extracorporeal treatments leading to contact of blood with negatively charged surfaces
  - Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney

SPECIAL WARNINGS AND PRECAUTIONS:

All warnings related to each component, as listed below, should apply also to the fixed combination of Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM).**

Special warnings

Lithium

The combination of lithium and the combination of perindopril / indapamide is usually not recommended.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes

The combination of perindopril and potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes is usually not recommended.

Neutropenia / agranulocytosis / thrombocytopenia/anemia

Neutropenia / agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (*e.g.* sore throat, fever).

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Hypersensitivity / angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including perindopril. This may occur at any time during treatment. In such cases perindopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway, should be administered promptly.
Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases, there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.
The combination of perindopril with sacubitril / valsartan is contraindicated due to the increased risk of angioedema. Sacubitril / valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril / valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril / valsartan. Concomitant use of ACE inhibitors with NEP inhibitors (*e.g.* racecadotril), mTOR inhibitors (*e.g.* sirolimus, everolimus, temsirolimus) and gliptins (*e.g.* linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (*e.g.* swelling of the airways or tongue, with or without respiratory impairment). Caution should be used when starting racecadotril, mTOR inhibitors (*e.g.* sirolimus, everolimus, temsirolimus) and gliptins (*e.g.* linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during desensitization

There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. ACE inhibitors should be used with caution in allergic patients treated with desensitization, and avoided in those undergoing venom immunotherapy. However, these reactions could be prevented by temporary withdrawal of ACE inhibitor for at least 24 hours before treatment in patients who require both ACE inhibitors and desensitization.

Anaphylactoid reactions during LDL apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Hemodialysis patients

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (*e.g.*, AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Primary aldosteronism

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic encephalopathy

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause, particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to coma. Administration of the diuretic should be stopped immediately if this occurs.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides and related thiazides 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

Renal function

- In cases of severe renal impairment (creatinine clearance < 30 mL/min), treatment is contraindicated.
- For patients with a moderate renal impairment (creatinine clearance < 60 mL/min), treatment is contraindicated with Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** doses containing 10mg/2.5mg of perindopril / indapamide combination (*i.e.*, Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** 10mg/2.5mg/5mg and 10mg/2.5mg/10mg).
- In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only. In these patients' usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.
  The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.
- Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc.): Marked stimulation of the renin-angiotensin-aldosterone system has been observed with perindopril particularly during marked water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with edema and ascites.
  The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset. In such cases, the treatment should then be initiated at a lower dose and increased progressively. In patients with ischemic heart or cerebrovascular disease an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
- Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25mg/l, *i.e.* 220 µmol/l for an adult).
  In the elderly the value of plasma creatinine levels should be adjusted in relation to age, weight and gender.
  Hypovolemia, secondary to the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.
- Amlodipine may be used at normal doses in patients with renal failure. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.
- The effect of the combination Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** has not been tested in renal dysfunction. In renal impairment, Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** doses should respect those of the individual components taken separately.

Hypotension and water and sodium depletion

- There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore, systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhea or vomiting. Regular monitoring of plasma electrolytes should be carried out in such patients. Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.
  Transient hypotension is not a contraindication to continuation of treatment. After reestablishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.
- Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in 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.

Potassium levels

- The combination of indapamide with perindopril and amlodipine does not prevent the onset of hypokalemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.
- Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril., ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (*e.g.*, spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (*e.g.* heparin, co-trimoxazole also known as trimethoprim / sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.
- Potassium depletion with hypokalemia is a major risk with thiazide diuretics and thiazide-related diuretics. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of lowered potassium levels (< 3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with edema and ascites, coronary patients and patients with heart failure. In such cases hypokalemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders. Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalemia, as with bradycardia, acts as a factor which favors the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal. In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment. If low potassium levels are detected, correction is required. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

Calcium levels

Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

Plasma magnesium:

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnaesemia.

Renovascular hypertension

The treatment for renovascular hypertension is revascularization. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.
If Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is prescribed to patients with known or suspected renal artery stenosis, treatment should be started in a hospital setting at a low dose and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

Cough

A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterized by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic etiology should be considered in the event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

Atherosclerosis

The risk of hypotension exists in all patients but particular care should be taken in patients with ischemic heart disease or cerebral circulatory insufficiency, with treatment being started at a low dose.

Hypertensive crisis

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Cardiac failure / severe cardiac insufficiency

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.
In patients with severe cardiac insufficiency (grade IV) treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

Aortic or mitral valve stenosis / hypertrophic cardiomyopathy

ACE inhibitors should be used with caution in patient with an obstruction in the outflow tract of the left ventricle.

Diabetic patients

In patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose.
The glycemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.
Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

Ethnic differences

As with other angiotensin converting enzyme inhibitors, perindopril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Surgery / anesthesia

Angiotensin converting enzyme inhibitors can cause hypotension in cases of anesthesia, especially when the anesthetic administered is an agent with hypotensive potential.
It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible one day before surgery.

Hepatic impairment

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.
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. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.
The effect of the combination Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** has not been tested in hepatic dysfunction. Taking into account the effect of each individual component of this combination, Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is contraindicated in patients with severe hepatic impairment, and caution should be exercised in patients with mild to moderate hepatic impairment.

Uric acid

Tendency to gout attacks may be increased in hyperuricemia patients.

Elderly

Renal function and potassium levels should be tested before the start of treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of water and electrolyte depletion, in order to avoid sudden onset of hypotension.

In the elderly increase of the dosage of amlodipine should take place with care.

Excipients
Level of sodium
Triplixam contains less than 1 mmol sodium (23mg) per tablet, *i.e.* essentially 'sodium-free'.

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.

Interaction with other medicinal products and other forms of interaction
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Drugs increasing the risk of angioedema:
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4). Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (*e.g.* sirolimus, everolimus, temsirolimus) and gliptins (*e.g.* linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema (see section 4.4).

Drugs inducing hyperkalaemia:
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with Triplixam. Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics (*e.g.* spironolactone, triamterene or amiloride), ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of these drugs increases the risk of hyperkalaemia. Therefore, the combination of Triplixam with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium

Concomitant use contraindicated (See section 4.3):
Aliskiren: In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal treatments: Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (*e.g.* polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Children and adolescents:
Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** should not be given to children and adolescents.

Pregnancy and Breastfeeding:
Given the effects of the individual components in this combination product on pregnancy and lactation, Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is not recommended during the first trimester of pregnancy. Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is contraindicated during the second and third trimesters of pregnancy.
Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** taking account the importance of this therapy for the mother.

Pregnancy
Perindopril:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contraindicated during the second and third trimesters of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension.

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.

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

Breastfeeding
Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** is not recommended during lactation.

Perindopril:
Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

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 breast-feeding, with a decrease or even suppression of milk lactation.

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
Common to perindopril and indapamide:
Reproductive toxicity studies showed no effect on fertility in female and male rats. No effects on human fertility are anticipated.

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 effects were found on male fertility.

Driving and using machines:
No studies on the effects of Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** on the ability to drive and use machines have been performed.
Perindopril and indapamide have no influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients.
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. As a result, the ability to drive or operate machinery may be impaired. Caution is recommended especially at the start of treatment.

DRUG INTERACTIONS:
Do not take aliskiren (used to treat hypertension) if patient has diabetes or kidney problems.
Avoid Perindopril arginine + Indapamide + Amlodipine (TRIPLIXAM) with:
- lithium (used to treat some mental disorders such as mania, manic depressive illness and recurrent depression),
- potassium-sparing drugs (*e.g.* triamterene, amiloride), potassium supplements or potassium-containing salt substitutes, other drugs which can increase potassium in your body (such as heparin, a medicine used to thin blood to prevent clots; trimethoprim and co-trimoxazole also known as trimethoprim/sulfamethoxazole for infections caused by bacteria),
- dantrolene (infusion) (used to treat malignant hyperthermia during anesthesia (symptoms including very high fever and muscle stiffness),
- estramustine (used in cancer therapy),
- medicines, which are most often used to treat diarrhea (racecadotril) or avoid rejection of transplanted organs (sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors).
- sacubitril/valsartan (used to treat long-term heart failure).
- other medicines used to treat high blood pressure: angiotensin-converting-enzyme inhibitor and angiotensin receptor blockers.

Special care may be required with:
- other medicines for treating high blood pressure, including angiotensin II receptor blocker (ARB), aliskiren, or diuretics (medicines which increase the amount of urine produced by the kidneys),
- potassium-sparing drugs used in the treatment of heart failure: eplerenone and spironolactone at doses between 12.5mg to 50mg by day,
- anesthetic medicines,
- iodinated contrast agent,
- bepridil (used to treat angina pectoris),
- methadone (used to treat addiction),
- medicines used for heart rhythm problems (*e.g.* dofetilide, ibutilide, bretylium, cisapride, diphemanil, procainamide, quinidine, hydroquinidine, disopyramide, amiodarone, sotalol,
- verapamil, diltiazem (heart medicines),
- digoxin or other cardiac glycosides (for the treatment of heart problems),
- antibiotics used to treat bacterial infections (*e.g.* rifampicin, erythromycin, clarithromycin, sparfloxacin, moxifloxacin,
- antifungal medicines (*e.g.* itraconazole, ketoconazole, amphotericin B by injection
- allopurinol (for the treatment of gout),
- antihistamines used to treat allergic reactions, such as hay fever (*e.g.* mizolastine, terfenadine, astemizole,
- corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis, and non-steroidal anti-inflammatory drugs (*e.g.* ibuprofen) or high dose salicylates (*e.g.* acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting),
- immunosuppressants (medicines used to control your body's immune response for the treatment of auto-immune disorders or following transplant surgery (*e.g.* ciclosporin, tacrolimus),
- tetracosactide (to treat Crohn's disease),
- gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis),
- halofantrine (used to treat certain types of malaria),
- baclofen used to treat muscle stiffness in diseases such as multiple sclerosis,
- medicines to treat diabetes such as insulin or metformin,
- calcium including calcium supplements,
- stimulant laxatives (*e.g.* senna),
- medicines for the treatment of cancer,
- vincamine (used to treat symptomatic cognitive disorders in elderly including memory loss),
- medicines used to treat mental disorders such as depression, anxiety, schizophrenia (*e.g.* tricyclic antidepressants, antipsychotics, imipramine like antidepressants, neuroleptics such as amisulpride, sulpride, sultopride, tiapride, haloperidol, droperidol),
- pentamidine (used to treat pneumonia),
- ritonavir, indinavir, nelfinavir (protease inhibitors used to treat HIV).
- *hypericum perforatum* (St. John's wort),
- trimethoprim (for the treatment of infections),
- medicines used for the treatment of low blood pressure, shock or asthma (*e.g.* ephedrine, noradrenaline or adrenaline),
- nitroglycerin and other nitrates, or other vasodilators that may further reduce blood pressure.

Perindopril arginine + Indapamide + Amlodipine (TRIPLIXAM) with food and drink:
Grapefruit juice and grapefruit should not be consumed by people who are taking Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)**. 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 this medicine.

ADVERSE DRUG REACTIONS:
Summary of the safety profile
The most commonly reported adverse reactions with perindopril, indapamide and amlodipine given separately are: hypokalaemia, dizziness, headache, paresthesia, somnolence, dysgeusia, visual impairment, diplopia, tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), cough, dyspnea, gastro-intestinal disorders (abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, change of bowel habit), pruritus, rash, rash maculopapular, muscle spasms, ankle swelling, asthenia, edema and fatigue.

Tabulated list of adverse reactions
The following undesirable effects have been observed with perindopril, indapamide or amlodipine during treatment and ranked under the following frequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Perindopril	Indapamide	Amlodipine
Infections and infestations	Rhinitis	Very rare	-	Uncommon
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare	-	
Blood and Lymphatic System Disorders	Eosinophilia	Uncommon*	-	-
	Agranulocytosis	Very rare	Very rare	-
	Aplastic anemia	-	Very rare	
	Pancytopenia	Very rare	-	-
	Leukopenia	Very rare	Very rare	Very rare
	Neutropenia	Very rare	-	-
	Hemolytic anemia	Very rare	Very rare	-
	Thrombocytopenia	Very rare	Very rare	Very rare
Immune System Disorders	Hypersensitivity	-	Uncommon	Very rare
Metabolism and Nutrition Disorders	Hypokalemia	-	Common	-
	Hypoglycemia	Uncommon*	-	-
	Hyperkalemia reversible on discontinuation	Uncommon*	-	-
	Hyponatremia	Uncommon*	Uncommon	
	Hypochloraemia	-	Rare	-
	Hypomagnesaemia	-	Rare	-
	Hyperglycemia	-	-	Very rare
	Hypercalcemia	-	Very rare	-
Psychiatric disorders	Insomnia	-	-	Uncommon
	Mood altered (including anxiety)	Uncommon	-	Uncommon
	Depression	Uncommon*	-	Uncommon
	Sleep disorder	Uncommon	-	-
	Confusional state	Very rare	-	Rare
Nervous System disorders	Dizziness	Common	-	Common
	Headache	Common	Rare	Common
	Paresthesia	Common	Rare	Uncommon
	Somnolence	Uncommon*	-	Common
	Hypoesthesia	-	-	Uncommon
	Dysgeusia	Common	-	Uncommon
	Tremor	-	-	Uncommon
	Syncope	Uncommon*	Not known	Uncommon
	Hypertonia	-	-	Very rare
	Neuropathy peripheral	-	-	Very rare
Nervous System disorders	Extrapyramidal disorder (extrapyramidal syndrome)	-	-	Not known
	Stroke possibly secondary to excessive hypotension in high-risk patients	Very rare	-	-
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency	-	Not known	-
Eye Disorders	Visual impairment	Common	Not known	Common
	Acute-angle closure glaucoma	-	Not known	-
	Choroidal effusion	-	Not known	-
	Diplopia	-	-	Common
	Myopia	-	Not known	-
	Vision blurred	-	Not known	-
Ear and labyrinth disorders	Tinnitus	Common	-	Uncommon
	Vertigo	Common	Rare	-
Cardiac Disorders	Palpitations	Uncommon*	-	Common
	Tachycardia	Uncommon*	-	-
	Angina pectoris	Very rare	-	-
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	Very rare	Uncommon
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients	Very rare	-	Very rare
	Torsade de pointes (potentially fatal)	-	Not known	-
Vascular Disorders	Flushing	Rare	-	Common
	Hypotension (and effects related to hypotension)	Common	Very rare	Uncommon
	Vasculitis	Uncommon*	-	Very rare
	Raynaud's phenomenon	Not known	-	-
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common	-	Uncommon
	Dyspnea	Common	-	Common
	Bronchospasm	Uncommon	-	-
	Eosinophilic pneumonia	Very rare	-	-
Gastro-intestinal Disorders	Abdominal pain	Common	-	Common
	Constipation	Common	Rare	Common
	Diarrhea	Common	-	Common
	Dyspepsia	Common	-	Common
	Nausea	Common	Rare	Common
	Vomiting	Common	Uncommon	Uncommon
	Dry mouth	Uncommon	Rare	Uncommon
	Change of bowel habit	-	-	Common
	Gingival hyperplasia	-	-	Very rare
	Pancreatitis	Very rare	Very rare	Very rare
	Gastritis	-	-	Very rare
Hepato-biliary Disorders	Hepatitis	Very rare	Not known	Very rare
	Jaundice	-	-	Very rare
	Hepatic function abnormal	-	Very rare	-
Skin and Subcutaneous Tissue Disorders	Pruritus	Common	-	Uncommon
	Rash	Common	-	Uncommon
	Rash maculopapular		Common	-
	Urticaria	Uncommon	Very rare	Uncommon
	Angioedema	Uncommon	Very rare	Very rare
	Alopecia	-	-	Uncommon
	Purpura	-	Uncommon	Uncommon
	Skin discoloration	-	-	Uncommon
	Hyperhidrosis	Uncommon	-	Uncommon
	Exanthema	-	-	Uncommon
	Photosensitivity reaction	Uncommon*	Not known	Very rare
	Psoriasis aggravation	Rare	-	-
	Pemphigoid	Uncommon*	-	-
	Erythema multiforme	Very rare	-	Very rare
	Stevens-Johnson Syndrome	-	Very rare	Very rare
	Exfoliative dermatitis	-	-	Very rare
	Toxic epidermal necrolysis	-	Very rare	Not known
	Quincke's edema	-	-	Very rare
Musculoskeletal And Connective Tissue Disorders	Muscle spasms	Common	Not known	Common
	Ankle swelling	-	-	Common
	Arthralgia	Uncommon *	-	Uncommon
	Muscular weakness	-	Not known	-
	Myalgia	Uncommon *	Not known	Uncommon
	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
	Anuria/Oliguria	Rare	-	-
	Acute renal failure	Rare	-	-
	Renal failure	Uncommon	Very rare	-
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon	Uncommon	Uncommon
	Gynecomastia	-	-	Uncommon
General Disorders and Administration Site Conditions	Asthenia	Common	-	Common
	Fatigue	-	Rare	Common
	Edema	-	-	Very common
	Chest pain	Uncommon*	-	Uncommon
	Pain	-	-	Uncommon
	Malaise	Uncommon*	-	Uncommon
	Edema peripheral	Uncommon*	-	-
	Pyrexia	Uncommon*	-	-
Investigations	Weight increased	-	-	Uncommon
	Weight decreased	-	-	Uncommon
	Blood urea increased	Uncommon*	-	-
	Blood creatinine increased	Uncommon*	-	-
	Blood bilirubin increased	Rare	-	-
	Hepatic enzyme increased	Rare	Not known	Very rare
	Hemoglobin decreased and hematocrit decreased	Very rare	-	-
	Electrocardiogram QT prolonged	-	Not known	-
	Blood glucose increased	-	Not known	-
	Blood uric acid increased	-	Not known	-
Injury, poisoning and procedural complications	Fall	Uncommon *	-	-

** Frequency calculated from clinical trials for adverse events detected from spontaneous report*

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 1.5mg: Plasma potassium < 3.4 mmol/l was seen in 10% of patients and < 3.2 mmol/l in 4% of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.
- Indapamide 2.5mg: 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 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.

OVERDOSE AND TREATMENT:
There is no information on overdosage with Perindopril arginine + Indapamide + Amlodipine **(TRIPLIXAM)** in humans.

For perindopril/indapamide combination:
Symptoms: The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

Management: The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialized center until they return to normal.
If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an intravenous infusion of isotonic saline may be given, or any other method of volemic expansion may be used.

Perindoprilat, the active form of perindopril, can be dialyzed.

For amlodipine:
Experience with intentional overdose in humans is limited.
Symptoms: Available data suggest that gross overdosage 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.
Management: Clinically significant hypotension due to amlodipine overdosage 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 10mg 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:
It is important to take the medicine every day as regular treatment is more effective. However, if a dose is forgotten, take the next dose at the usual time. Do not take a double dose to make up for the 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, pharmacist or nurse.

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 tablet container. The expiry date refers to the last day of that month.

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

PACKAGING:
Thirty (30) film-coated tablets in polypropylene tablet container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant.

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

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.

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