SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Triplixam 5 mg/1.25 mg/5 mg film-coated tablet
[Triplixam 5 mg/1.25 mg/10 mg film-coated tablet]
[Triplixam 10 mg/2.5 mg/5 mg film-coated tablet]
[Triplixam 10 mg/2.5 mg/10 mg film-coated tablet]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 3.395 mg perindopril equivalent to 5 mg perindopril arginine, 1.25 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg of amlodipine.
[One film-coated tablet contains 3.395 mg perindopril equivalent to 5 mg perindopril arginine, 1.25 mg indapamide and 13.870 mg amlodipine besilate equivalent to 10mg of amlodipine].
[One film-coated tablet contains 6.790 mg perindopril equivalent to 10 mg perindopril arginine, 2.5 mg indapamide and 6.935 mg amlodipine besilate equivalent to 5 mg of amlodipine].
[One film-coated tablet contains 6.790 mg perindopril equivalent to 10 mg perindopril arginine, 2.5 mg indapamide and 13.870 mg amlodipine besilate equivalent to 10 mg of amlodipine].
For one film-coated tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Triplixam 5/1.25/5 mg: White, oblong, film-coated tablet, 9.75 mm long and 5.16 mm wide, engraved with  on one face and  on the other face.
Triplixam 5/1.25/10 mg: White, oblong, film-coated tablet, 10.7 mm long and 5.66 mm wide, engraved with  on one face and  on the other face.
Triplixam 10/2.5/5 mg: White, oblong, film-coated tablet, 11.5 mm long and 6.09 mm wide, engraved with  on one face and  on the other face.
Triplixam 10/2.5/10 mg: White, oblong, film-coated tablet, 12.2 mm long and 6.46 mm wide, engraved with  on one face and  on the other face.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Triplixam is indicated as substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril/indapamide fixed dose combination and amlodipine, taken simultaneously at the same dose level.

4.2. Posology and method of administration

Posology
One 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

Patients with renal impairment (see sections 4.3 and 4.4)
In severe renal impairment (creatinine clearance below 30 mL/min), treatment is contraindicated.
In patients with moderate renal impairment (creatinine clearance 30-60 mL/min), Triplixam at the doses 10 mg/2.5 mg /5 mg and 10 mg/2.5 mg/10 mg 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 (glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2) (see section 4.3).

Patients with hepatic hepatic impairment (see sections 4.3, 4.4 and 5.2)
In severe hepatic impairment, Triplixam is contraindicated.

In patients with mild to moderate hepatic impairment, Triplixam should be administrated with caution, as dosage recommendations for amlodipine have not yet been established.

Elderly (see section 4.4)
Elimination of perindoprilat is decreased in the elderly (see section 5.2).
Elderly can be treated with Triplixam according to renal function (see section 4.3).

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

Method of administration

Oral use.

4.3. 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 Triplixam doses containing 10 mg/2.5 mg of perindopril/indapamide combination (i.e., Triplixam 10 mg/2. 5mg/5 mg and 10 mg/2.5 mg/10 mg).
- Hypersensitivity to the active substances, to other sulphonamides, to dihydropyridine derivatives, any other ACE inhibitor or to any of the excipients listed in section 6.1.
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy (see section 4.4).
- Hereditary/idiopathic angioedema.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Hepatic encephalopathy.
- Severe hepatic impairment.
- Hypokalaemia.
- Severe hypotension.
- Shock, including cardiogenic shock.
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Concomitant use of Triplixam with aliskiren-containing products is contra-indicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Perindopril-containing treatment must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).

- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).

4.4. Special warnings and precautions for use

All warnings related to each component, as listed below, should apply also to the fixed combination Triplixam.

Special warnings

Lithium
The combination of lithium and the combination of perindopril/indapamide is usually not recommended (see section 4.5).

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 impairment of 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 (see sections 4.5 and 5.1).
However, 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 diuretics, potassium supplements or potassium-containing salt substitutes
The combination of perindopril and potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes is usually not recommended (see section 4.5).

Neutropenia/agranulocytosis/thrombocytopenia/anaemia
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other risk 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 risk 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, regular monitoring of blood count (white blood cell count) is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever) (see section 4.8).

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see section 4.3). 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 ACE 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 until complete resolution of symptoms. 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 oedema 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 1/1,000 (0.3 mL to 0.5 mL) and/or measures to ensure a patent airway, should be administered promptly. Black patients 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 (see section 4.3).

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, 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 (see section 4.3). 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 (see sections 4.3 and 4.5). 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) (see section 4.5). 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 desensitisation

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

Anaphylactoid reactions during low density lipoprotein (LDL) apheresis

Rarely, patients receiving ACE inhibitors during LDL apheresis with adsorption on dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed 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 hyperaldosteronism

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 in these patients.

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 a well 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 (see sections 4.3 and 4.6).

Hepatic encephalopathy

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

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Precautions for use

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 Triplixam doses containing 10 mg/2.5 mg of perindopril /indapamide combination (i.e., Triplixam 10 mg/2.5 mg /5 mg and 10 mg/2.5 mg/10 mg).
- 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 with renal artery stenosis.
- The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.
- Risk of hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc.): marked stimulation of the RAAS 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 oedema and ascites.
  The blocking of this system with an ACE 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 be initiated at a lower dose and increased progressively. In patients with ischaemic heart or cerebrovascular disease, a major 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 25 mg/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.
  Hypovolaemia, 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 consequence in patients with normal renal function but may 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 Triplixam has not been tested in renal dysfunction. In renal impairment, Triplixam doses should respect those of the individual components taken separately.

Hypotension and water and electrolytes 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 diarrhoea 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 re-establishment 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 (see sections 4.8 and 4.9).
  Any diuretic treatment may cause hyponatraemia, sometimes with serious consequences.
  Hyponatraemia associated with hypovolaemia may be responsible of dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to a secondary compensatory metabolic alkalosis: the incidence and degree of this effect are low.

Potassium levels

- The combination of indapamide with perindopril and amlodipine does not prevent the onset of hypokalaemia 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 hyperkalaemia include renal insufficiency, alteration of renal function, age (> 70 years), diabetes mellitus, intercurrent events, such as dehydratation, acute cardiac decompensation, metabolic acidosis or concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, potassium-containing salt substitutes or other drugs associated with increases in serum potassium (e.g. heparin, cotrimoxazole 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 perindopril and any of the above mentioned agents is deemed necessary, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).
- Potassium depletion with hypokalaemia 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 hypokalaemia (< 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 oedema and ascites, coronary patients and patients with heart failure.
- In such cases hypokalaemia 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.
  Hypokalaemia, as with bradycardia, acts as a factor which favours 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.

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 (see section 4.8).

Renovascular hypertension

The treatment for renovascular hypertension is revascularisation. Nonetheless, ACE inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.

If 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 ACE inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an ACE inhibitor is essential, continuation of treatment may be considered.

Atherosclerosis

The risk of hypotension exists in all patients but particular care should be taken in patients with ischaemic 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 have not been established.

Cardiac failure

Patients with heart failure should be treated with caution.

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

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 glycaemia levels should be closely monitored in diabetic patients treated with oral antidiabetic drugs or insulin, especially 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 specificities

As with other ACE 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 / anaesthesia

ACE inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is an agent with hypotensive potential.

It is therefore recommended that treatment with long-acting ACE 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 may progress 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 (see section 4.8).

The half-life of amlodipine is prolonged and area under the curve (AUC) values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be

initiated at the lowest dose 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 Triplixam has not been tested in hepatic dysfunction. Taking into account the effect of each individual component of this combination, 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 hyperuricaemic 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 (see sections 4.2 and 5.2).

Excipients
Level of sodium
Triplixam contains less than 1 mmol sodium (23 mg) per tablet,that is 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.

4.5. Interaction with other medicinal products and other forms of interaction

Clinical trial data has shown that dual blockade of the 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 impaired 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 risk for occurrence of hyperkalaemia, such as 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.

- **Extra-corporeal treatments**

Extracorporeal treatments leading to contact of blood with negatively charged surfaces, such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile membranes) and LDL apheresis with dextran sulphate, are contraindicated, due to a risk of 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.

Concomitant use not recommended

Component	***Known interaction with the following product***	***Interaction with other medicinal product***
perindopril / indapamide	Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of perindopril combined with indapamide with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).
perindopril	Aliskiren	In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase (see section 4.4).
	Concomitant therapy with ACE inhibitor and angiotensin II receptor blocker	It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with ACE inhibitor and angiotensin II receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening of renal function (including acute renal failure) as compared to use of a single RAAS agent. Dual blockade (e.g by combining an ACE inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.
	Estramustine	Risk of increased adverse effects such as angioneurotic oedema (angioedema).
	Potassium-sparing diuretics (e.g. triamterene, amiloride), potassium (salts)	Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of perindopril with these drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see section "Concomitant use which requires special care".
amlodipine	Dantrolene (infusion)	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to develop malignant hyperthermia and in the management of malignant hyperthermia.
	Grapefruit or grapefruit juice	The bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Concomitant use which requires special care

Component	*Known interaction with the following product*	*Interaction with other medicinal product*
perindopril indapamide	Baclofen	Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.
	NSAIDs (including acetylsalicylic acid at high doses)	When ACE inhibitors are administered simultaneously with NSAIDs (such as acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including a risk of acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
perindopril	Antidiabetic agents (insulin, oral hypoglycaemic agents)	Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appears to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.
	Non potassium-sparing diuretics	Patients on diuretics, and especially those who are volume and/or salt depleted, may experience marked reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril. In hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE inhibitor (in which case a non potassium-sparing diuretic can be thereafter reintroduced) or the ACE inhibitor must be initiated with a low dosage and progressively increased. In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dosage, after reducing the dosage of the associated non potassium-sparing diuretic. In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor therapy.
	Potassium-sparing diuretics (eplerenone, spironolactone)	With eplerenone or spironolactone at doses between 12.5 mg and 50 mg by day and with low doses of ACE inhibitors: In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40%, and previously treated with ACE inhibitors and loop diuretics, there is a risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination. Before initiating the combination, check the absence of hyperkalaemia and renal impairment. A close monitoring of the kalaemia and creatininaemia is recommended once a week in the first month of the treatment and monthly thereafter.
indapamide	Drugs inducing torsades de pointes	Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicinal products that induce torsades de pointes such as, but not limited to: • class Ia antiarrhythmic agents (e.g. quinidine, hydroquinidine, disopyramide); • class III antiarrhythmic agents (e.g. amiodarone, dofetilide, ibutilide, bretylium, sotalol); • some antipsychotics: Phenothiazines (e.g. chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine). Benzamides (e.g. amisulpride, sulpiride, sultopride, tiapride), Butyrophenones (e.g. droperidol, haloperidol), Other antipsychotics (e.g. pimozide) • other substances (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, vincamine IV, methadone, astemizole, terfenadine). Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

Component	*Known interaction with the following product*	*Interaction with other medicinal product*
	Amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives	Increased risk of low potassium levels (additive effect). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non stimulant laxatives should be used.
	Cardiac glycosides	Low potassium levels favour the toxic effects of cardiac glycosides. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.
	Allopurinol	Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.
amlodipine	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, St John's wort [*Hypericum perforatum*]).
	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 plasma concentration. The clinical translation of these PK 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.

Concomitant use to be taken into consideration:

Component	*Known interaction with the following product*	*Interaction with other medicinal product*
perindopril / indapamide / amlodipine	Imipramine-like antidepressants (tricyclics), neuroleptics	Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).
	Other antihypertensive agents	Use of other antihypertensive medicinal products could result in additional blood pressure lowering effect.
	Corticosteroids, tetracosactide	Reduction in antihypertensive effect (salt and water retention due to corticosteroids).
perindopril	Antihypertensive agents and vasodilators	Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.
	Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide	Concomitant administration with ACE inhibitors may lead to an increased risk for leukopenia.
	Anaesthetic drugs	ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs.
	Diuretics (thiazide or loop diuretics)	Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.
	Sympathomimetics	Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors
	Gold	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Component	*Known interaction with the following product*	*Interaction with other medicinal product*
indapamide	Metformin	Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed 15 mg/l (135 µmol/L) in men and 12 mg/L (110 micromol/l) in women.
	Iodinated contrast media	In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.
	Calcium (salts)	Risk of increased levels of calcium due to reduced elimination of calcium in the urine.
	Ciclosporine	Risk of increased creatinine levels with no change in circulating levels of ciclosporine, even when there is no salt and water depletion.
amlodipine	Atorvastatin, digoxin or warfarin	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.
	Ciclosporin	No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0 % - 40 %) of ciclosporin were observed. Consideration should be given to monitoring ciclosporin levels in renal transplant patients on amlodipine, and ciclosporin dose reductions should be made as necessary.
	Simvastatin	Co-administration of multiple doses of 10 mg of amlodipine with 80 mg of simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

4.6. Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation, Triplixam is not recommended during the first trimester of pregnancy. Triplixam is contraindicated during the second and third trimesters of pregnancy.
Triplixam is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Triplixam taking into account the importance of this therapy for the mother.

Pregnancy

Linked to perindopril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological data regarding the risk of malformation following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive ; however a small increase in risk of congenital malformation cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have a well 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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, foetal ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken ACE inhibitors should be closely observed for blood pressure level (see sections 4.3 and 4.4).

Linked to indapamide
There is no data or limited data (less than 300 pregnancy outcomes) on the use of indapamide in pregnant women. Prolonged exposure to thiazide diuretics during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foetoplacental ischaemia and growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported following exposure near term.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Linked to amlodipine
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Breastfeeding

Triplixam is not recommended during breastfeeding.

Linked to perindopril
Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with well established safety profiles during breastfeeding are preferable, especially while nursing a new-born or preterm infant.

Linked to indapamide
There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulphonamide-derived medicines and hypokalaemia might occur. A risk for new-borns/infants cannot be excluded.
Indapamide is closely related to thiazide diuretics which have been associated, during breastfeeding, with 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 to 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.

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 effects were found on male fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies on the effects of 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 treated with amlodipine suffer from dizziness, headache, fatigue, weariness or nausea, their ability to react may be impaired.
As a result the ability to drive or use machines may be impaired. Caution is recommended especially at the start of treatment.

4.8. Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions with perindopril, indapamide and amlodipine given separately are: dizziness, headache, paraesthesia, somnolence, dysgeusia, visual impairment, diplopia, tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), cough, dyspnoea, gastrointestinal disorders (abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting, change of bowel habit), pruritus, rash, rash maculopapular, muscle spasms, ankle swelling, asthenia, oedema and fatigue.

List of undesirable effects

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
Blood and Lymphatic System Disorders	Eosinophilia	Uncommon*	-	-
	Agranulocytosis (see section 4.4)	Very rare	Very rare	-
	Aplastic anaemia	-	Very rare	-
	Pancytopenia	Very rare	-	-
	Leukopenia (see section 4.4)	Very rare	Very rare	Very rare
	Neutropenia (see section 4.4)	Very rare	-	-
	Haemolytic anaemia	Very rare	Very rare	-
	Thrombocytopenia (see section 4.4)	Very rare	Very rare	Very rare
Immune System Disorders	Hypersensitivity	-	Uncommon	Very rare
Metabolism and Nutrition Disorders	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon*	-	-
	Hyperkalaemia reversible on discontinuation (see section 4.4)	Uncommon*	-	-
	Hyponatraemia (see section 4.4)	Uncommon*	Not known	-
	Hyperglycaemia	-	-	Very rare
	Hypercalcaemia	-	Very rare	-
	Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4)	-	Not known	-
Psychiatric disorders	Insomnia	-	-	Uncommon
	Mood altered (including anxiety)	Uncommon	-	Uncommon
	Depression	-	-	Uncommon
	Sleep disorder	Uncommon	-	-
	Confusional state	Very rare	-	Rare
Nervous System disorders	Dizziness	Common	-	Common
	Headache	Common	Rare	Common
	Paraesthesia	Common	Rare	Uncommon

	Somnolence	Uncommon*	-	Common
	Hypoaesthesia	-	-	Uncommon
	Dysgeusia	Common	-	Uncommon
	Tremor	-	-	Uncommon
	Syncope	Uncommon*	Not known	Uncommon
	Hypertonia	-	-	Very rare
	Neuropathy peripheral	-	-	Very rare
	Extrapyramidal disorder (extrapyramidal syndrome)	-	-	Not known
	Stroke, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare	-	-
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4)	-	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 (see section 4.4)	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 (see section 4.4)	Very rare	-	Very rare
	Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)	-	Not known	-
Vascular Disorders	Flushing	-	-	Common
	Hypotension (and effects related to hypotension) (see section 4.4)	Common	Very rare	Uncommon
	Vasculitis	Uncommon*	-	Very rare
	Raynaud's phenomenon	Not known	-	-
Respiratory, Thoracic and Mediastinal Disorders	Cough (see section 4.4)	Common	-	Uncommon
	Dyspnoea	Common	-	Common
	Bronchospasm	Uncommon	-	-
	Eosinophilic pneumonia	Very rare	-	-
Gastrointestinal Disorders	Abdominal pain	Common	-	Common
	Constipation	Common	Rare	Common
	Diarrhoea	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	Hepatitis (see section 4.4)	Very rare	Not known	Very rare

Disorders	Jaundice	-	-	Very rare
	Hepatic function abnormal	-	Very rare	-
Skin and Subcutaneous Tissue Disorders	Pruritus	Common	-	Uncommon
	Rash	Common	-	Uncommon
	Rash maculopapular		Common	-
	Urticaria (see section 4.4)	Uncommon	Very rare	Uncommon
	Angioedema (see section 4.4)	Uncommon	Very rare	Very rare
	Alopecia	-	-	Uncommon
	Purpura	-	Uncommon	Uncommon
	Skin discolouration	-	-	Uncommon
	Hyperhidrosis	Uncommon	-	Uncommon
	Exanthema	-	-	Uncommon
	Photosensitivity reaction	Uncommon*	Not known (see section 4.4)	Very rare
	Psoriasis aggravation	Rare	-	-
	Pemphigoid	Uncommon*	-	-
	Erythema multiform	Very rare	-	Very rare
	Stevens-Johnson Syndrome	-	Very rare	Very rare
	Exfoliative dermatitis	-	-	Very rare
	Toxic epidermal necrolysis	-	Very rare	Not known
	Quincke's oedema	-	-	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
	Acute renal failure	Very rare	-	-
	Renal failure	Uncommon	Very rare	-
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon	-	Uncommon
	Gynaecomastia	-	-	Uncommon
General Disorders and Administration Site Conditions	Asthenia	Common	-	Common
	Fatigue	-	Rare	Common
	Oedema	-	-	Very common
	Chest pain	Uncommon*	-	Uncommon
	Pain	-	-	Uncommon
	Malaise	Uncommon*	-	Uncommon
	Oedema 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
	Haemoglobin decreased and haematocrit decreased (see section 4.4)	Very rare	-	-
	Electrocardiogram QT prolonged (see sections 4.4 and 4.5)	-	Not known	-
	Blood glucose increased	-	Not known	-
	Blood uric acid increased	-	Not known	-
Injury, poisoning and procedural complications	Fall	Uncommon *	-	-

** Frequency estimated from clinical trial data for the undesirable effects reported post-marketing as spontaneous notifications.*

Cases of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy, including perindopril.

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.

4.9. Overdose

There is no information on overdose with Triplixam in humans.

Concerning perindopril/indapamide combination

Symptoms

For perindopril/indapamide combination, 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 hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

Treatment

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 specialised centre 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 volaemic expansion may be used.
Perindoprilat, the active form of perindopril, can be dialysed (see section 5.2).

Concerning amlodipine

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.

Treatment

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, combinations. ACE inhibitors, calcium channel blockers and diuretics. ATC code: C09BX01
Triplixam is a combination of three antihypertensive components with complementary mechanisms to control blood pressure in patient with hypertension. Perindopril arginine salt is an ACE inhibitor, indapamide, a chlorosulphamoyl diuretic and amlodipine, a calcium ion flux inhibitor of the dihydropyridine group.
The pharmacological properties of 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

Linked to perindopril
Perindopril is an inhibitor of the angiotensin converting enzyme (ACE) which converts angiotensin I to angiotensin II, a vasoconstricting substance, and stimulates the secretion of aldosterone by the adrenal cortex and 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 muscular and renal areas, 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 after-load.

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 muscles.

Exercise test results also showed improvement.

Linked to indapamide
Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide 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.

Linked to 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 muscles.

Pharmacodynamic effects

Linked to perindopril/indapamide
In hypertensive patients regardless of age, the perindopril/indapamide combination exerts a dose-dependent antihypertensive 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 comparison to each of the products administered alone.

Linked to 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 the ACE 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 artery trunks, corrects histomorphometric changes in 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 ACE inhibitor with a thiazide diuretic also decreases the hypokalaemia risk associated with the diuretic alone.

Linked to 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.

Linked to 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 ischaemic burden by the following two actions:

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (after-load) 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 dilation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's angina).

In patients with hypertension, once daily dosing of amlodipine provides clinically significant reduction of blood pressure in both the supine and standing positions throughout the 24 hour interval. The progressive action of amlodipine prevents hypotension attacks.
Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Clinical efficacy and safety

Triplixam has not been studied on morbidity and mortality.

Linked to perindopril/indapamide
PICXEL, a multicentre, randomised, double blind active controlled study has assessed by echocardiography the effect of a monotherapy perindopril/indapamide combination on left ventricular hypertrophy (LVH) versus enalapril.
In PICXEL, hypertensive patients with LVH (defined as left ventricular mass index (LVMI) > 120 g/m^2 in men and > 100 g/m^2 in women) were randomised either to perindopril tert-butylamine 2 mg (equivalent to perindopril arginine 2.5 mg)/indapamide 0.625 mg or to enalapril 10 mg once a day for a one-year treatment. The dose could be adapted according to blood pressure control, up to perindopril tert-butylamine 8 mg (equivalent to perindopril arginine 10 mg) and indapamide 2.5 mg or enalapril 40 mg once a day. Only 34 % of the subjects remained treated with perindopril tert-butylamine 2 mg (equivalent to perindopril arginine 2.5 mg)/indapamide 0.625 mg (versus 20 % with enalapril 10 mg).
At the end of treatment, LVMI had decreased significantly more in the perindopril/indapamide group (-10.1 g/m²) than in the enalapril group (-1.1 g/m²) in the all randomised patients population. The between group difference in LVMI change was -8.3 g/m² (95% CI (-11.5,-5.0), p < 0.0001).
A better effect on LVMI was reached with the 8 mg perindopril/indapamide doses (equivalent to perindopril arginine 10 mg)/indapamide 2.5 mg.
Regarding blood pressure, the estimated mean between-group differences in the randomised population were -5.8 mmHg (95 % CI (-7.9, -3.7), p < 0.0001) for systolic blood pressure and -2.3 mmHg (95 % CI (-3.6, -0.9), p = 0.0004) for diastolic blood pressure, in favour of the perindopril/indapamide group.

The ADVANCE study was a multicentre, international, randomised, 2x2 factorial designed trial and aimed at determining the benefits of blood pressure lowering with the fixed combination perindopril/indapamide vs placebo on top of current standard therapy (double blind comparison) and of gliclazide MR based intensive glucose control strategy (HbA1c target of 6.5 % or lower) vs standard glucose control (PROBE [Prospective Randomised Open study with Blinded Evaluation] design) on macrovascular and microvascular events in type 2 diabetic patients.
The primary end-point was a composite of major macrovascular (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) and microvascular (new or worsening nephropathy and retinopathy) events.
Overall, 11,140 type 2 diabetic patients (mean values: age 66 years, BMI 28 kg/m^2, duration of diabetes 8 years, HbA1c 7.5 % and SBP/DBP 145/81 mmHg) were involved in the trial. Among them, 83 % were hypertensive, 32 % and 10% presented a history of macro- or micro- vascular disease respectively and 27 % had microalbuminuria. Concomitant therapies included BP lowering agents (75 %), lipid lowering agents (35 % mainly statins 28 %), aspirin or other antiplatelets (47 %).
Following a 6-week open run-in period on perindopril/indapamide combination and usual glucose lowering treatment, patients were randomly assigned to placebo (n=5,571) or perindopril/indapamide combination (n=5,569).
After a mean duration of follow-up of 4.3 years, the treatment with perindopril/indapamide resulted in a significant relative risk reduction of 9 % in the primary endpoint (95 % CI [0.828;0.996], p=0.041).
This benefit was driven by a significant relative risk reduction of 14 % in total mortality (95% CI [0.75;0.98], p=0.025), of 18% in cardiovascular deaths (95% CI [0.68;0.98], p=0.027) and of 21% in total renal events (95% CI [0.74;0.86], p < 0.001) in the perindopril/indapamide group compared to the placebo group.
In the sub-group of interest of hypertensive patients, there was a relative risk reduction of 9 % in the combined major macrovascular and microvascular events in the perindopril/indapamide group compared to the placebo group (95% CI [0.82;1.00], p=0.052).

There were also a significant relative risk reduction of 16 % in total mortality (95% CI [0.73;0.97], p=0.019), of 20 % in cardiovascular deaths (95% CI [0.66;0.97], p=0.023) and of 20 % in total renal events (95% CI [0.73;0.87], p < 0.001) in the perindopril/indapamide group compared to the placebo group.
The benefits of the BP lowering intervention were independent of those observed with the intensive glucose control strategy.

Linked to amlodipine
A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare recent drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.
A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrolment) or documentation of other atherosclerotic CVD (overall 51.5 %), type 2 diabetes (36.1 %), HDL-C < 35 mg/dL (11.6 %), LVH diagnosed by electrocardiogram or echocardiography (20.9 %), current smoking (21.9 %).
The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 (95 % CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7 %, RR 1.38, (95 % CI [1.25-1.52] p < 0.001)). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 (95 % CI [0.89-1.02] p=0.20).

Dual blockade of the RAAS clinical trial data
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of combination of an ACE inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study performed in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed.
Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers.

ACE inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, with or without cardiovascular disease. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and certain serious adverse events (such as hyperkalaemia, hypotension and renal impairment) were more frequently reported in the aliskiren group than in the placebo group.

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

5.2. Pharmacokinetic properties

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

Linked to 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 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 ACE, but is concentration-dependent.

Biotransformation
Perindopril is a prodrug. Bioavailability of perindoprilat, the active metabolite, is 27 %. 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 (see sections 4.2 and 4.4).

Linked to 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 %.

Biotransformation 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 faeces (22 %) in the form of inactive metabolites.

Special populations
The pharmacokinetics is unchanged in patients with renal insufficiency.

Linked to 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.

Biotransformation
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 is available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine due to a longer half-life and an increase in AUC of approximately 40-60 %.

5.3. Preclinical safety data

Perindopril
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.
No mutagenicity has been observed in in vitro or in vivo studies.
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, ACE inhibitors, as a class, have been shown to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. Fertility was not impaired either in male or in female rats.
No carcinogenicity has been observed in long term studies in rats and mice.

Indapamide
The highest doses administered orally to different animal species (40 to 8,000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms observed during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, *i.e*. bradypnoea and peripheral vasodilation.
Indapamide has been tested negative concerning mutagenic and carcinogenic properties.
Reproductive toxicity studies have not shown any embryotoxic or teratogenic effect in rats, mice and rabbits.
Fertility was not impaired either in male or female rats.

Perindopril/indapamide
The perindopril/indapamide combination has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in rats. However, the combination produces gastrointestinal toxicity in dogs and increased toxic effects in the mother in rats (compared to perindopril).
Nonetheless, these adverse effects appear at dose levels much higher than the therapeutic doses.
Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

Amlodipine

Reproductive toxicity studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.
Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
*Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core
Calcium carbonate starch compound: Calcium carbonate 90 %, Pregelatinised maize starch 10 %
Cellulose microcrystalline (E460).
Croscarmellose sodium (E468).
Magnesium stearate(E572).
Colloidal anhydrous silica.
Pregelatinised starch.

Film-coating
Glycerol (E422).
Hypromellose 6PC (E464).
Macrogol 6000.
Magnesium stearate (E572).
Titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

For the containers of 28 and 30 film-coated tablets, the in-use stability after first opening is 30 days.
For the container of 100 film-coated tablets, the in-use stability after first opening is 100 days.

6.4. Special precautions for storage

Store below 30°C. Store in the original package.
Keep the container tightly closed in order to protect from moisture.

6.5. Nature and contents of container

10, 28 or 30 film-coated tablets in a polypropylene tablet container equipped with a low density polyethylene flow reducer and a low density polyethylene stopper containing a desiccant.

100 film-coated tablets in a high density polyethylene tablet container equipped with a polypropylene stopper containing a desiccant.

Box of 10, 28, 30, 60 (2 tablet containers of 30), 84 (3 tablet containers of 28), 90 (3 tablet containers of 30), 100, 500 tablets (5 tablet containers of 100).

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER
50, RUE CARNOT
92284 SURESNES CEDEX - FRANCE

8. MANUFACTURER

SERVIER (IRELAND) INDUSTRIES LTD
GOREY ROAD
ARKLOW - CO. WICKLOW – IRELAND

9. DATE OF REVISION OF THE TEXT

06.2021