

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prestalia 3.5 mg/2.5 mg tablets

[Prestalia 7 mg/5 mg tablets]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 2.378 mg perindopril equivalent to 3.5 mg perindopril arginine and 3.4675 mg amlodipine besilate equivalent to 2.5 mg amlodipine.

[One tablet contains 4.756 mg perindopril equivalent to 7 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine]

Excipient with known effect: 31.62 mg lactose monohydrate.

[Excipient with known effect: 63.23 mg lactose monohydrate.]

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, round tablet, 5 mm diameter.

[White, round tablet, 6 mm diameter, engraved with  on one face.]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prestalia is indicated for the treatment of essential hypertension in adults.

4.2 Posology and method of administration

Posology

Oral use.

Prestalia 3.5 mg/2.5 mg is intended for first line therapy in patients with arterial hypertension.

The recommended starting dose of Prestalia is 3.5 mg/2.5 mg once daily.

After at least four weeks of treatment, the dose may be increased to 7 mg/5 mg once daily in patients whose blood pressure is not adequately controlled with Prestalia 3.5 mg/2.5 mg.

Special populations

Patients with renal impairment (see sections 4.3, 4.4 and 5.2)

Prestalia is contraindicated in patients with severe renal impairment (Creatinine clearance below 30 ml/min) (see section 4.3).

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Prestalia is 3.5 mg/2.5 mg every other day. In patients whose blood pressure is not adequately controlled, the dose of Prestalia 3.5 mg/2.5 mg may be taken once daily. If necessary, the dose may be increased in patients insufficiently controlled. The usual medical follow-up includes monitoring of creatinine and potassium (see sections 4.4 and 5.2).

Patients with hepatic impairment (see sections 4.4 and 5.2)

Caution should be exercised when prescribing Prestalia to patients with severe hepatic impairment.

Older people (see sections 4.4 and 5.2)

The efficacy and safety of Prestalia have been established in older people. Caution should be exercised at initiation depending on renal function.

After initiation of the treatment, renal function should be monitored before increase of the dosage, particularly in patients aged 75 years and above. The usual medical follow-up should include monitoring of creatinine and potassium.

Paediatric population

The safety and efficacy of Prestalia in children aged below 18 years have not been established. No data are available.

Method of administration

The tablet of Prestalia should be taken as a single dose, preferably in the morning and before a meal.

4.3 Contraindications

- Hypersensitivity to the active substances, to ACE inhibitors, to dihydropyridines derivatives, or to any of the excipients listed in section 6.1,
- Severe renal impairment (see sections 4.2 and 4.4),
- History of angioedema associated with previous ACE inhibitor therapy,
- Hereditary or idiopathic angioedema,
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6),
- 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 Prestalia with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5),
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney (see section 4.4).
- Concomitant use with sacubitril/valsartan [therapy, Perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan](#) (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Special warnings

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Prestalia should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was 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, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving Prestalia (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, 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 (see section 4.8).

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. Concomitant use of other NEP inhibitors (e.g. racecadotril) and ACE inhibitors may also increase the risk of angioedema (see section 4.5). Hence, a careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):-

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

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

Anaphylactoid reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

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 complicating factors, neutropenia occurs rarely. Prestalia 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 Prestalia is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

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 (see sections 4.5 and 5.1).

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.

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:

Prestalia should not be initiated during pregnancy. Unless continued Prestalia is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Prestalia should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Use in patients with renal impairment:

Prestalia is contra-indicated in patients with severe renal impairment (Creatinine clearance below 30 ml/min) (see section 4.3).

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Prestalia is 3.5 mg/2.5 mg every other day (see section 4.2). The usual medical follow-up in such patients should include monitoring of potassium levels and creatinine (see sections 4.2 and 5.2).

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment.

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

Kidney transplantation:

Since there is no experience regarding the administration of Prestalia in patients with a recent kidney transplantation, treatment with Prestalia is therefore not recommended.

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 (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.

Use in patients with impaired hepatic function:

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 Prestalia who develop jaundice or marked elevations of hepatic enzymes should discontinue Prestalia and receive appropriate medical follow-up (see section 4.8).

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function.

Use in older people:

Initiation and increase of the dosage should take place with care in older people, depending on renal function. Renal function should be monitored before increase of the dosage. Therefore, the medical follow-up should include monitoring of potassium and creatinine (see sections 4.2 and 5.2).

Precautions for use

Hypertensive crisis:

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

Use in patients with cardiac failure:

Patients with heart failure should be treated with caution.

Prestalia should be used with caution in patients with congestive heart failure, as amlodipine may increase the risk of future cardiovascular events and mortality.

Hypotension:

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with Prestalia.

Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:

ACE inhibitors should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Race:

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

ACE inhibitors may be 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.

Cough:

Cough has been reported with the use of Prestalia. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia:

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. Prestalia should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalemia:

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. 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, alone or in combination), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, other ACE inhibitors, angiotensin-II antagonists, acetylsalicylic acid \geq 3 g/day, COX-2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and co-trimoxazole also known as trimethoprim/sulfamethoxazole). 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. If concomitant use of Prestalia and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Diabetic patients:

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with Prestalia (see section 4.5).

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

The combination of Prestalia and potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes is not recommended (see section 4.5).

Excipients:

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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/Medicines 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:

Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and Co-trimoxazole (trimethoprim/sulfamethoxazole). The combination of Prestalia with these drugs increases the risk of hyperkalaemia (see section 4.4). Therefore, the combination of Prestalia 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 contra-indicated (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.

Sacubitril/valsartan

The concomitant use of perindopril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. 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 not recommended (see section 4.4):

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). ACE inhibitors must not be associated with hyperkalaemic substances, except in hypokalaemia.

The combination of Prestalia with the above-mentioned 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 below.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of Prestalia with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Dantrolene (infusion):

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of Prestalia containing amlodipine, a calcium channel blocker, be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Concomitant use which requires special care:

Antidiabetic agents (insulins, 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 appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Baclofen:

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics:

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive 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 Prestalia.

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, the diuretic must be discontinued before initiating Prestalia, in which case a non-potassium-sparing diuretic can be thereafter reintroduced.

Renal function (creatinine levels) must be monitored during the first few weeks of Prestalia therapy.

Potassium-sparing diuretics (eplerenone, spironolactone):

With eplerenone or spironolactone at doses between 12.5 mg to 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, 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 creatininemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including aspirin ≥ 3 g/day:

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of Prestalia and NSAIDs may lead to an increased risk of worsening of renal function, including possible 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.

Ciclosporin

[Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.](#)

Heparin

[Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.](#)

Racecadotril

ACE inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a drug used against acute diarrhea) (see section 4.4).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus):

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin):

[Increased risk of angio-oedema, due to dipeptidyl peptidase IV \(DPP-IV\) decreased activity by the gliptin, in patients co-treated with an ACE inhibitor.](#)

CYP3A4 inducers:

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

CYP3A4 inhibitors:

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant

increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and Prestalia 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 which requires some care:

Antihypertensive agents (such as beta-blockers) and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of Prestalia. Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

Gliptines (linagliptine, saxagliptine, sitagliptine, vildagliptine):

~~Increased risk of angio-oedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptine, in patients co-treated with an ACE inhibitor.~~

Tricyclic antidepressants/Antipsychotics/Anaesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with Prestalia may result in further reduction of blood pressure.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of Prestalia.

Corticosteroids, tetracosactide:

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin):

Increased antihypertensive effect and increased risk of orthostatic hypotension.

Amifostine:

May potentiate the antihypertensive effect of amlodipine.

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.

Grapefruit:

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

Tacrolimus:

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

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Ciclosporine:

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

4.6 Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation: Prestalia is not recommended during the first trimester of pregnancy. Prestalia is contraindicated during the second and third trimesters of pregnancy.

Prestalia is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Prestalia taking 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 contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

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 antihypertensive 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 foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to ACE inhibitor 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 (see sections 4.3 and 4.4).

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). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding:

Linked to 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.

Linked to amlodipine:

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother..

Fertility:

Linked to perindopril:

There was no effect on reproductive performance or fertility.

Linked to amlodipine:

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse 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 Prestalia on the ability to drive and use machines have been performed.

Perindopril and 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. Caution is recommended with Prestalia especially at the start of treatment.

4.8 Undesirable effects

Summary of the safety profile:

The safety profile of Prestalia has been evaluated on a 6-month controlled study involving 1,771 patients, 887 of whom received Prestalia, a 6-week controlled study involving 837 patients, 279 of whom received Prestalia, and an 8-week placebo-controlled study involving 1581 patients, 249 of whom received Prestalia.

In these clinical studies, no significant new adverse reactions were observed with the combination compared to the known effects of the individual monocomponents.

The following adverse reactions were found to be the most frequently reported during clinical trials: dizziness, cough and oedema.

The adverse drug reactions previously reported during clinical trials and/or post-marketing experience with one of the individual components of Prestalia (perindopril and amlodipine) have been listed in the following table since they may occur with the fixed-dose combination.

Tabulated list of adverse reactions:

The following undesirable effects have been observed during treatment with Prestalia, perindopril or amlodipine given separately and ranked under the MedDRA classification by body system and under the following frequency:

Very common ($\geq 1/10$) ; common ($\geq 1/100$ to $< 1/10$) ; uncommon ($\geq 1/1000$ to $< 1/100$) ; rare ($\geq 1/10000$ to $< 1/1000$) ; very rare ($< 1/10000$) ; not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Prestalia (Perindopril/ Amlodipine)	Amlodipine	Perindopril
Infections and infestations	Rhinitis	-	Uncommon	Very rare
Blood and the lymphatic	Eosinophilia	-	-	Uncommon*
	Leukopenia/neutropenia (see section 4.4)	-	Very rare	Very rare

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Prestalia (Perindopril/ Amlodipine)	Amlodipine	Perindopril
System Disorders	Agranulocytosis or pancytopenia (see section 4.4)	-	-	Very rare
	Thrombocytopenia (see section 4.4)	-	Very rare	Very rare
	Haemolytic anaemia enzyme specific in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	-	Very rare
Immune System Disorders	Hypersensitivity	-	Very rare	Uncommon
Metabolism and Nutrition Disorders	Hyperkalaemia (see section 4.4)	Uncommon	-	Uncommon*
	Hyperglycaemia	Uncommon	Very rare	-
	Hyponatraemia	-	-	Uncommon*
	Hypoglycaemia (see sections 4.4 and 4.5)	-	-	Uncommon*
Psychiatric Disorders	Mood altered (including anxiety)	-	Uncommon	Uncommon
	Insomnia	-	Uncommon	-
	Depression	-	Uncommon	-
	Sleep disorder	-	-	Uncommon
	Confusional state	-	Rare	Very rare
Nervous System Disorders	Dizziness (especially at the beginning of the treatment)	Common	Common	Common
	Headache (especially at the beginning of the treatment)	-	Common	Common
	Somnolence (especially at the beginning of the treatment)	-	Common	Uncommon*
	Dysgeusia	-	Uncommon	Common
	Paraesthesia	-	Uncommon	Common
	Syncope	-	Uncommon	Uncommon*
	Hypoesthesia	-	Uncommon-	-
	Tremor	-	Uncommon	-
	Hypertonia	-	Very rare	-
	Neuropathy peripheral	-	Very rare	-
	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	-	Very rare
	Extrapyramidal disorder (extrapyramidal syndrome)	-	Not known	-
Eye Disorders	Visual impairment	-	Common	Common
	Diplopia	-	Common	-
Ear and	Tinnitus	-	Uncommon	Common

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Prestalia (Perindopril/Amlodipine)	Amlodipine	Perindopril
labyrinth Disorders	Vertigo	-	-	Common
Cardiac Disorders	Palpitations	-	Common	Uncommon*
	Tachycardia	-	-	Uncommon*
	Angina pectoris	-	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	-	Very rare	Very rare
	Arrythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	-	Uncommon	Very rare
Vascular Disorders	Flushing	-	Common	-
	Hypotension (and effects related to hypotension)	-	Uncommon	Common
	Vasculitis	-	Very Rare	Uncommon*
	Raynaud's phenomenon	-	-	Not known
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common	Uncommon	Common
	Dyspnoea	-	Common	Common
	Bronchospasm	-	-	Uncommon
	Eosinophilic pneumonia	-	-	Very rare
Gastro-intestinal Disorders	Abdominal pain	-	Common	Common
	Nausea	-	Common	Common
	Vomiting	-	Uncommon	Common
	Dyspepsia	-	Common	Common
	Diarrhoea	-	Common	Common
	Constipation	-	Common	Common
	Change of bowel habit	-	Common	-
	Dry mouth	-	Uncommon	Uncommon
	Gingival hyperplasia	-	Very rare	-
	Pancreatitis	-	Very rare	Very rare
	Gastritis	-	Very rare	-
Hepato-biliary Disorders	Hepatitis, jaundice	-	Very rare	-
	Hepatitis either cytolytic or cholestatic (see section 4.4)	-	-	Very rare
Skin and Subcutaneous Tissue Disorders	Rash, exanthema	-	Uncommon	Common
	Pruritus	-	Uncommon	Common
	Hyperhidrosis	-	Uncommon	Uncommon

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Prestalia (Perindopril/ Amlodipine)	Amlodipine	Perindopril
	Alopecia	-	Uncommon	-
	Purpura	-	Uncommon	-
	Skin discolouration	-	Uncommon	-
	Pemphigoid	-	-	Uncommon*
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	-	Very rare	Uncommon
	Urticaria	-	Uncommon	Uncommon
	Photosensitivity reaction	-	Very rare	Uncommon*
	Erythema multiforme	Uncommon	Very rare	Very rare
	Quincke's oedema	-	Very rare	-
	Stevens-Johnson Syndrome	-	Very rare	-
	Exfoliative dermatitis	-	Very rare	-
	Toxic Epidermal Necrolysis	-	Not known	-
	Psoriasis aggravation	-	-	Rare
Musculoskeletal And Connective Tissue Disorders	Back pain	-	Uncommon	-
	Joint swelling (ankle swelling)	-	Common	-
	Muscle spasms	-	Common	Common
	Arthralgia, myalgia	-	Uncommon	Uncommon*
Renal and Urinary Disorders	Micturition disorder, nocturia, pollakiuria	-	Uncommon	-
	Renal failure	-	-	Uncommon
	Renal failure acute	-	-	Very rare
Reproductive System and Breast Disorders	Erectile dysfunction	-	Uncommon	Uncommon
	Gynaecomastia	-	Uncommon	-
General Disorders and Administration Site Conditions	Oedema peripheral	Common	-	Uncommon*
	Oedema	-	Very common	-
	Fatigue	Uncommon	Common	-
	Asthenia	-	Common	Common
	Chest pain	-	Uncommon	Uncommon*
	Malaise	-	Uncommon	Uncommon*
	Pain	-	Uncommon	-
	Pyrexia	-	-	Uncommon*
Investigations	Weight increased, weight decreased	-	Uncommon	-

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Prestalia (Perindopril/ Amlodipine)	Amlodipine	Perindopril
	Blood urea increased	-	-	Uncommon*
	Blood creatinine increased	-	-	Uncommon*
	Blood bilirubin increased	-	-	Rare
	Hepatic enzyme increased	-	Very rare	Rare
	Haemoglobin decreased and haematocrit decreased	-	-	Very rare
Injury, poisoning and procedural complications	Fall	-	-	Uncommon*

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

Cases of 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.

Additional information on the combination perindopril/amlodipine:

A randomised, double-blind, placebo-controlled study over 8 weeks demonstrated that peripheral oedema, a recognised side effect of amlodipine, was observed at a lower incidence in patients who received the perindopril 3.5 mg/amlodipine 2.5 mg combination than in those who received amlodipine 5 mg alone (1.6% and 4.9% respectively).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

There is no experience of overdose with Prestalia.

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 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 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.

For perindopril, limited data are available for overdosage in humans. Symptoms associated with the overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the systemic circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors and calcium channel blockers, ATC code: C09BB04.

Mechanism of action:

Prestalia combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and perindopril to the angiotensin converting enzyme inhibitors class of medicines.

The combination of these substances has an additive antihypertensive effect.

Pharmacodynamic effects:

Perindopril:

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

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.

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 (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 ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Clinical efficacy and safety:

Perindopril/Amlodipine:

In an 8-week multicenter, randomised, double-blind, placebo-controlled, parallel group factorial study of 1581 patients with mild to moderate hypertension, perindopril 3.5 mg/amlodipine 2.5 mg clinically and statistically

significantly reduced mean systolic/diastolic blood pressure (SBP/DBP) by 22.0/13.6 mmHg as compared to placebo (14.2/9.3 mmHg), perindopril 3.5 mg (16.3/9.7 mmHg) and amlodipine 2.5 mg (16.0/10.3 mmHg) ($p < 0.001$ for all comparisons).

In a 6-month, multicentre, randomised, double-blind, active-controlled study, 1,774 patients with mild to moderate hypertension received either perindopril 3.5 mg/amlodipine 2.5 mg, uptitrated to 7 mg/5 mg, and 14 mg/10 mg, then to 14 mg/10 mg combined with indapamide 1.5 mg, or a valsartan-amlodipine strategy (valsartan 80 mg uptitrated to 160 mg and to valsartan/amlodipine 160 mg/5 mg, then to valsartan/amlodipine 160 mg/10 mg).

At 3 months, Prestalia strategy showed clinically and statistically significant mean decrease in SBP/DBP (25.9/16.9 mmHg) as compared to valsartan-amlodipine strategy (23.6/15.5 mmHg) ($p < 0.001$ for all comparisons).

Blood pressure was controlled in 56.4% of patients treated with Prestalia strategy *versus* 49.0% with valsartan-amlodipine strategy ($p = 0.002$), and the rate of responders was 87.4% *versus* 81.6%, respectively ($p < 0.001$).

The superiority of Prestalia strategy over the valsartan-amlodipine strategy on blood pressure decrease and responder rates was observed from 1 month and maintained at each visit up to 6 months.

These results were confirmed in a 24-hour automated blood pressure monitoring (ABPM) performed in a subset of 1029 patients. At 3 months and 6 months, the decrease of the mean SBP and DBP over 24 hours was greater with Prestalia (15.5/9.4 mmHg and 17/10.4 mmHg, respectively) as compared to valsartan-amlodipine strategy (12.7/8.0 mmHg and 14.7/9.2 mmHg, respectively) ($p \leq 0.001$).

In the 8-month open-label follow-up on 1,554 patients, the safety profile of Prestalia was in line with the safety profiles of perindopril and amlodipine.

In a 9-month multicentre, randomised, double-blind, active-controlled study, 3,270 patients with mild to severe hypertension received either perindopril /amlodipine 3.5 mg/2.5 mg, uptitrated to 7 mg/5 mg, 14 mg/5 mg then 14 mg/10 mg, or an irbesartan-hydrochlorothiazide strategy (irbesartan 150 mg, then irbesartan/hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg).

The proportion of patients with controlled blood pressure statistically significantly increased with each of the perindopril/amlodipine treatment dose over each evaluation period ($p < 0.001$ until 3 months, and $p \leq 0.003$ until 6 months).

After 6 months of treatment, the mean decrease in blood pressure was similar in the perindopril/amlodipine group (22.0/10.1 mmHg) and the irbesartan-hydrochlorothiazide group (22.5/9.6 mmHg) for both SBP ($p = 0.116$) and DBP ($p = 0.050$).

The most common adverse reactions in clinical trials were dizziness, cough and oedema (see section 4.8).

The adverse reactions reported in clinical trials were in agreement with those anticipated from the safety profiles of the components perindopril and amlodipine.

Dual blockade of the renin-angiotensin-aldosterone system (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 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, cardiovascular disease, or both. 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 serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

The rate and extent of absorption of perindopril and amlodipine from Prestalia are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine from individual tablet formulations.

Perindopril:

Absorption:

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

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.

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.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

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.

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.

Amlodipine:

Absorption, distribution, plasma protein binding:

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation, elimination:

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

Special populations:

Paediatric population (age below 18 years):

No pharmacokinetic data are available in the paediatric population.

Older people:

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

Initiation and increase of the dosage should take place with care in older people depending on renal function. Elimination of perindoprilat is decreased in the elderly. Renal function should be monitored before increase of the dosage. Therefore, the usual medical follow-up will include monitoring of creatinine and potassium (see sections 4.2 and 4.4).

Renal impairment

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Prestalia is 3.5 mg/2.5 mg every other day (see section 4.2).

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Amlodipine is not dialyzable.

Elimination of perindoprilat is decreased in patients with heart or renal failure.

Therefore, the usual medical follow-up will include monitoring of creatinine and potassium (see sections 4.2 and 4.4).

Hepatic impairment

Caution should be exercised in patients with liver disease (see sections 4.2 and 4.4).

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%.

Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis: 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).

5.3 Preclinical safety data

Perindopril/Amlodipine:

A preclinical safety study has demonstrated that the combination of perindopril and amlodipine was well tolerated in rats. The findings from the 13-week oral toxicity study in rats were consistent with those of perindopril and amlodipine when both active substances are administered alone. There were no new toxicities or increased severity of the toxicities which were associated with either component.

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, angiotensin converting enzyme 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.

No carcinogenicity has been observed in long term studies in rats and mice. Fertility was not impaired either in male or in female rats.

Amlodipine:

Reproductive toxicology:

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

Impairment of fertility:

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a

dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis:

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

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Cellulose, microcrystalline (E460),
Silica, colloidal anhydrous (E551),
Magnesium stearate (E470B).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Tablet container of 10 tablets: Once opened, Prestalia should be used within 10 days.

Tablet container of 28 or 30 tablets: Once opened, Prestalia should be used within 30 days.

Tablet container of 100 tablets: Once opened, Prestalia should be used within 90 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

10, 28, 30 or 100 tablets in polypropylene tablet container equipped with a low density polyethylene stopper containing a desiccant gel (silica) and a low density polyethylene flow reducer.

Box of 1 tablet container of 10 tablets.

Box of 1 tablet container of 28 tablets.

Box of 3 tablet containers of 28 tablets.

Box of 1 tablet container of 30 tablets.

Box of 2 tablet containers of 30 tablets.

Box of 3 tablet containers of 30 tablets.

Box of 1 tablet container of 100 tablets.

Box of 5 tablet containers of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

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

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: {DD month YYYY}
<Date of latest renewal: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}
{DD/MM/YYYY}
{DD month YYYY}

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Prestalia 3.5 mg/2.5 mg tablets
perindopril arginine/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 2.378 mg perindopril equivalent to 3.5 mg perindopril arginine and 3.4675 mg amlodipine besilate equivalent to 2.5 mg amlodipine.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

10 tablets

28 tablets

30 tablets

60 tablets (2 tablet containers of 30)

84 tablets (3 tablet containers of 28)

90 tablets (3 tablet containers of 30)

100 tablets

500 tablets (5 tablet containers of 100)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

Tablet container of 10 tablets: Use within 10 days of opening.

Tablet container of 28 or 30 tablets: Use within 30 days of opening.

Tablet container of 100 tablets: Use within 90 days of opening.

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

To be completed nationally

For RMS (Italy):

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex - France

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

[To be completed nationally]

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Prestalia 3.5 mg/2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Prestalia 3.5 mg/2.5 mg tablets
perindopril arginine/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 2.378 mg perindopril equivalent to 3.5 mg perindopril arginine and 3.4675 mg amlodipine besilate equivalent to 2.5 mg amlodipine.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

10 tablets
28 tablets
30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

Tablet container of 10 tablets: Use within 10 days of opening.

Tablet container of 28 or 30 tablets: Use within 30 days of opening.

Tablet container of 100 tablets: Use within 90 days of opening.

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally
For RMS (Italy):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex - France

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.
[To be completed nationally]

15. INSTRUCTIONS ON USE

16. OTHER

Abbreviations for days of the week

MON
TUE
WED
THU
FRI
SAT
SUN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Prestalia 7 mg/5 mg tablets
perindopril arginine/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 4.756 mg perindopril equivalent to 7 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

10 tablets

28 tablets.

30 tablets

60 tablets (2 tablet containers of 30)

84 tablets (3 tablet containers of 28)

90 tablets (3 tablet containers of 30)

100 tablets

500 tablets (5 tablet containers of 100)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

Tablet container of 10 tablets: Use within 10 days of opening.

Tablet container of 28 or 30 tablets: Use within 30 days of opening.

Tablet container of 100 tablets: Use within 90 days of opening.

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

To be completed nationally

For RMS (Italy):

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex - France

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

[To be completed nationally]

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Prestalia 7 mg/5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Prestalia 7 mg/5 mg tablets
perindopril arginine/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One tablet contains 4.756 mg perindopril equivalent to 7 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet.

10 tablets
28 tablets.
30 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

Tablet container of 10 tablets: Use within 10 days of opening.

Tablet container of 28 or 30 tablets: Use within 30 days of opening.

Tablet container of 100 tablets: Use within 90 days of opening.

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

For RMS (Italy):

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex - France

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. OTHER

Abbreviations for days of the week

MON

TUE

WED

THU

FRI

SAT

SUN

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Prestalia 3.5 mg/2.5mg tablets
Prestalia 7 mg/5 mg tablets
perindopril arginine / amlodipine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

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

What is in this leaflet:

1. What Prestalia is and what it is used for
2. What you need to know before you take Prestalia
3. How to take Prestalia
4. Possible side effects
5. How to store Prestalia
6. Contents of the pack and other information

1. What Prestalia is and what it is used for

Prestalia is a combination of two active ingredients, perindopril and amlodipine. Both of these substances help to control your high blood pressure.

Perindopril is an ACE (Angiotensin Converting Enzyme) inhibitor. Amlodipine is a calcium antagonist (which belongs to a class of medicines called dihydropyridines). Together they work to widen and relax the blood vessels so that blood passes through them more easily and makes it easier for your heart to maintain a good blood flow.

Prestalia is used to treat high blood pressure (hypertension) in adults.

2. What you need to know before you take Prestalia

Do not take Prestalia

- if you are allergic (hypersensitive) to perindopril or any other ACE inhibitor, or to amlodipine or any other calcium antagonists, or any of the other ingredients of this medicine (listed in section 6),
- if you have severe kidney problems,
- if you have experienced symptoms such as wheezing, swelling of the face or tongue, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema),
- if you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body),
- if you have severe low blood pressure (hypotension),
- if you suffer from heart failure after a heart attack,
- if you are more than 3 months pregnant (it is also better to avoid Prestalia in early pregnancy – see pregnancy section),

- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren,
- if you are having dialysis or any other type of blood filtration. Depending on the machine that is used, Prestalia may not be suitable for you,
- if you have kidney problems where the blood supply to your kidneys is reduced (renal artery stenosis).
- if you have taken or are currently taking~~if you are being treated with~~ sacubitril/valsartan, a medicine for heart failure, as the risk of angioedema (rapid swelling under the skin in an area such as the throat) is increased. (see “Warning and Precaution” and “Other medicines and ~~Viaoram~~Prestalia”).

Warnings and precautions

Talk to your doctor or pharmacist or nurse before taking Prestalia if you:

- have hypertrophic cardiomyopathy (cardiac muscle disease),
- have heart failure,
- have severe increase in blood pressure (hypertensive crisis),
- have any other heart problems,
- have liver problems,
- have kidney problems (including kidney transplantation),
- have abnormally increased levels of a hormone called aldosterone in your blood (primary aldosteronism),
- have collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma,
- have diabetes,
- are on a salt restricted diet or use salt substitutes which contain potassium (a well balanced potassium blood level is essential),
- are elderly and your dose needs to be increased,
- are taking any of the following medicines used to treat high blood pressure:
 - o an “angiotensin II receptor blocker” (ARBs) (also known as sartans - for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems.
 - o aliskiren.

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

- See also information under the heading “Do not take Prestalia”.
- are of black origin since you may have a higher risk of angioedema and this medicine may be less effective in lowering your blood pressure than in non-black patients,
- are taking any of the following medicines, the risk of angioedema is increased:
 - racecadotril (used to treat diarrhea)
 - sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors (used to avoid rejection of transplanted organs and for cancer).
 - sacubitril (available as fixed dose combination with valsartan) used to treat long-term heart failure)
 - linagliptin, saxagliptin, sitagliptin, vildagliptin and other drugs belonging to the class of the also called gliptins (used to treat diabetes).

Angioedema:

Angioedema (a severe allergic reaction with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing) has been reported in patients treated with ACE inhibitors, including perindopril. This may occur at any time during treatment. If you develop such symptoms, you should stop taking Prestalia and see a doctor immediately. See also section 4.

You must tell your doctor if you think you are (or might become) pregnant. Prestalia is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

When you are taking Prestalia, you should also inform your doctor or the medical staff if you:

- are going to have a general anaesthetic and/or major surgery,
- have recently suffered from diarrhoea or vomiting (being sick),
- are to undergo LDL apheresis (the removal of cholesterol from your blood by a machine)
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings.

Children and adolescents

Prestalia should not be given to children and adolescents.

Other medicines and Prestalia

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

You should avoid Prestalia with:

- lithium (used to treat mania or depression),
- estramustine (used in cancer therapy),
- 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, medicine used to thin blood [to prevent clots](#), trimethoprim and co-trimoxazole also known as trimethoprim/sulfamethoxazole, for the treatment of infections [and ciclosporin, an immunosuppressant medicine used to prevent organ transplant rejection](#)),
- aliskiren (used to treat high blood pressure), (see also information under the headings “Do not take Prestalia” and “Warnings and precautions”),
- angiotension II -receptor blockers (ARB) (used to treat high blood pressure) (e.g. valsartan, telmisartan, irbesartan...),
- dantrolene (infusion) (used to treat muscle stiffness in diseases such as multiple sclerosis or to treat malignant hyperthermia during anaesthesia, symptoms including very high fever and muscle stiffness).
- Sacubitril/valsartan (used to treat long-term heart failure). See sections “Do not take [ViaeoramPrestalia](#)” and “Warnings and precautions”.

Treatment with Prestalia can be affected by other medicines. Make sure to tell your doctor if you are taking any of the following medicines as special care may be required:

- other medicines for high blood pressure, including diuretics (medicines which increase the amount of urine produced by the kidneys),
- 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). See section “Warnings and precautions”,
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or high dose aspirin,
- medicines to treat diabetes (such as insulin, gliptins),
- medicines to treat mental disorders such as depression, anxiety, schizophrenia etc (e.g. tricyclic antidepressants, antipsychotics, imipramine-like antidepressants, neuroleptics),
- immunosuppressants (medicines which reduce the defence mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporine, tacrolimus),
- allopurinol (for the treatment of gout),
- procainamide (for the treatment of an irregular heart beat),
- vasodilators including nitrates (products that widen the blood vessels),
- ephedrine, noradrenaline or adrenaline (medicines used to treat low blood pressure, shock or asthma),
- baclofen used to treat muscle stiffness in diseases such as multiple sclerosis,
- some antibiotics such as rifampicin, erythromycin, clarithromycin (for infection caused by bacteria),
- antiepileptic agents such as carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone,
- itraconazole, ketoconazole (medicines used for treatment of fungal infections),
- alpha-blockers used for the treatment of enlarged prostate such as prazosin, alfuzosin, doxazosin, tamsulosin, terazosin,
- amifostine (used to prevent or reduce side effects caused by other medicines or radiation therapy that are used to treat cancer),

- corticosteroids (used to treat various conditions including severe asthma and rheumatoid arthritis),
- gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis),
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV),
- potassium-sparing drugs used in the treatment of heart failure: eplerenone and spironolactone at doses between 12.5 mg to 50 mg by day,
- hypericum perforatum (St John's wort, an herbal medicine used to treat depression).

Prestalia with food and drink

See section 3.

Grapefruit juice and grapefruit should not be consumed by people who are taking Prestalia. 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 Prestalia.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Prestalia before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Prestalia. Prestalia is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding

Amlodipine has been shown to pass into breast milk in small amounts. Tell your doctor if you are breast-feeding or about to start breast-feeding. Prestalia is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Prestalia may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy, weak or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

Prestalia contains lactose monohydrate

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

3. How to take Prestalia

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

The recommended dose is one tablet of Prestalia 3.5 mg/2.5 mg once daily.

If you suffer from moderate kidney problems, your doctor may advise you to take one tablet of Prestalia 3.5 mg/2.5 mg every other day at the start of the treatment.

Depending on how you respond to the treatment, your doctor may decide to increase the dose after one month to Prestalia 7 mg/5 mg once a day if required.

One tablet of Prestalia 7 mg/5 mg once a day is the maximum recommended dose for high blood pressure.

Take your tablet preferably at the same time each day, in the morning, before a meal.

Do not exceed the prescribed dose.

If you take more Prestalia than you should

If you take too many tablets, contact your nearest accident and emergency department or tell your doctor immediately. The most likely effect in case of overdose is low blood pressure which can make you feel dizzy or faint. If this happens, lying down with your legs raised can help.

If you forget to take Prestalia

It is important to take your medicine every day as regular treatment works better. However, if you forget to take a dose of Prestalia, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Prestalia

As the treatment with Prestalia is usually life-long, you should discuss with your doctor before you stop taking your tablets.

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

4. Possible side effects

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

Stop taking the medicinal product and see a doctor immediately, if you experience any of the following side effects that can be serious:

- sudden wheeziness, chest pain, shortness of breath, or difficulty in breathing (bronchospasm) (Uncommon– may affect up to 1 in 100 people),
- swelling of eyelids, face or lips (Uncommon- may affect up to 1 in 100 people),
- swelling of the tongue and throat, which causes great difficulty breathing (angioedema) (Uncommon– may affect up to 1 in 100 people),
- severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching (erythema multiforme) (Very rare - may affect up to 1 in 10,000 people), blistering, peeling and swelling of the skin (exfoliative dermatitis) (Very rare - may affect up to 1 in 10,000 people), inflammation of mucous membranes (Stevens Johnson Syndrome) (Very rare- may affect up to 1 in 10,000 people), Toxic Epidermal Necrolysis (Not known) or other allergic reactions (Uncommon - may affect up to 1 in 100 people),
- severe dizziness or fainting due to low blood pressure (Common - may affect up to 1 in 10 people),
- weakness of arms or legs, or problems speaking which could be a sign of a possible stroke (Very rare - may affect up to 1 in 10,000 people),
- heart attack, chest pain (angina) (Very rare - may affect up to 1 in 10,000 people), unusual fast or abnormal heart beat (Common - may affect up to 1 in 10 people),
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell (Very rare - may affect up to 1 in 10,000 people),
- yellowing of the skin or eyes (jaundice) which could be a sign of hepatitis (Very rare - may affect up to 1 in 10,000 people).

The following **side effects** have been reported with Prestalia. If any of these cause you problems, you should **contact your doctor:**

- Common (may affect up to 1 in 10 people): light-headedness, cough, oedema (fluid retention).
- Uncommon side effects (may affect up to 1 in 100 people): high levels of blood potassium which can cause abnormal heart rhythm (hyperkalaemia), excess sugar in the blood (hyperglycaemia), tiredness.

The following **side effects** have been reported with perindopril or amlodipine, and either not observed with Prestalia or observed with a higher frequency than with Prestalia. These side effects may also occur with Prestalia. If any of these cause you problems, you should **contact your doctor**:

- Very common side effects (may affect more than 1 in 10 people): oedema (fluid retention).
- Common side effects (may affect up to 1 in 10 people): headache, sleepiness (especially at the beginning of treatment), abnormal taste perception, numbness or tingling sensation in your limbs, vertigo, vision disturbances (including double vision), tinnitus (sensation of noises in the ears), palpitations (awareness of your heartbeat), flushing, shortness of breath (dyspnoea), abdominal pain, nausea (feeling sick), vomiting (being sick), dyspepsia or difficulty of digestion, change of bowel habit, constipation, diarrhoea, itching, skin rashes, redness of the skin, pruritus, ankle swelling, muscle cramps, tiredness, weakness.
- Uncommon side effects (may affect up to 1 in 100 people): increase in some white blood cells (eosinophilia), low sodium level in the blood (hyponatraemia), low sugar level in the blood (hypoglycaemia), mood swings, anxiety, sleeplessness, depression, sleep disturbances, syncope, loss of pain sensation, trembling, vasculitis (inflammation of blood vessels), rhinitis (blocked up or runny nose), dry mouth, increased sweating, hair loss, red patches on skin, skin discolouration, formation of blister clusters over the skin, sensitivity to light, back pain, muscle or joint pain, disorder in passing urine, increased need to urinate at night, increased number of times of passing urine, kidney problems, impotence, discomfort or enlargement of the breasts in men, chest pain, feeling unwell, pain, weight increase or decrease, increased blood urea, increased blood creatinine, fall, fever.
- Rare side effects (may affect up to 1 in 1000 people): confusion, psoriasis worsening, high level of serum bilirubin, increased level of liver enzymes.
- Very rare side effects (may affect up to 1 in 10,000 people): changes in blood values such as a lower number of white and red blood cells, lower haemoglobin, lower number of blood platelets, increased muscle tension, disorders of the nerves which can cause weakness, tingling or numbness, eosinophilic pneumonia (a rare type of pneumonia), swelling of the gums, abdominal bloating (gastritis), yellowing of the skin (jaundice), acute renal failure.
- Frequency not known (frequency cannot be estimated from the available data): trembling, rigid posture, mask-like face, slow movements and a shuffling, unbalanced walk, discoloration, numbness and pain in fingers or toes (Raynaud's phenomenon).

Concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion can occur with ACE inhibitors. If you have these symptoms contact your doctor as soon as possible.

Reporting of side effects

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

5. How to store Prestalia

Keep out of the sight and reach of children.

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

This medicine does not require any special storage conditions.

Once opened, Prestalia should be used within 10 days for tablet containers of 10 tablets, 30 days for tablet containers of 28 or 30 tablets and 90 days for tablet containers of 100 tablets.

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

6. Contents of the pack and other information

What Prestalia contains:

- The active substances are perindopril arginine and amlodipine.
One tablet of Prestalia 3.5 mg/2.5 mg contains 2.378 mg perindopril equivalent to 3.5 mg perindopril arginine and 3.4675 mg amlodipine besilate equivalent to 2.5 mg amlodipine.
One tablet of Prestalia 7 mg/5 mg contains 4.756 mg perindopril equivalent to 7 mg perindopril arginine and 6.935 mg amlodipine besilate equivalent to 5 mg amlodipine.
- The other ingredients are: lactose monohydrate, magnesium stearate (E470B), cellulose microcrystalline (E460), colloidal anhydrous silica (E551).

What Prestalia looks like and contents of the pack:

Prestalia 3.5 mg/2.5 mg tablets are white, round tablets, 5 mm diameter.

Prestalia 7 mg/5 mg tablets are white, round tablets, 6 mm diameter, engraved with  on one face.

The tablets of Prestalia 3.5 mg/2.5 mg and Prestalia 7 mg/5 mg are available in packs containing 10, 28, 30, 60 (2 tablet containers of 30), 84 (3 tablet containers of 28), 90 (3 tablet containers of 30), 100 or 500 (5 tablet containers of 100) tablets.

The dessicant is present in the stopper of the tablet containers.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacture r

Marketing Authorisation Holder:

<[To be completed nationally]>

For RMS (Italy):

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex - France

Manufacturer:

Servier (Ireland) Industries Ltd

Gorey Road

Arklow - Co. Wicklow – Ireland

and

Les Laboratoires Servier Industrie

905, route de Saran

45520 Gidy - France

and

Anpharm Przedsiębiorstwo Farmaceutyczne S.A.
Ul. Annopol 6B
03-236 Warsaw – Poland

and

Egis Pharmaceuticals Private Limited Company
Site 3: H-9900, Körmend
Mátyás király u. 65. – Hungary

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

Estonia	Prestalia
Greece	Prestalia, δισκία
Hungary	Covercard, tableta
Italy	Prestalia, compresse
Latvia	Prestalia, tabletes

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

[To be completed nationally]

<Other sources of information>

<Detailed information on this medicine is available on the website of {MS/Agency}>