PROFESSIONAL INFORMATION

PEARLOC RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PEARLOC 4 mg/5 mg tablets.

PEARLOC 4 mg/10 mg tablets.

PEARLOC 8 mg/5 mg tablets.

PEARLOC 8 mg/10 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PEARLOC 4 mg/5 mg: Each tablet contains perindopril tert-butylamine 4 mg and amlodipine besilate equivalent to amlodipine 5 mg.

PEARLOC 4 mg/10 mg: Each tablet contains perindopril tert-butylamine 4 mg and amlodipine besilate equivalent to amlodipine 10 mg.

PEARLOC 8 mg/5 mg: Each tablet contains perindopril tert-butylamine 8 mg and amlodipine besilate equivalent to amlodipine 5 mg.

PEARLOC 8 mg/10 mg: Each tablet contains perindopril tert-butylamine 8 mg and amlodipine besilate equivalent to amlodipine 10 mg.

PEARLOC tablets are sugar free.

PEARLOC tablets are essentially ‘sodium free’.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

PEARLOC 4 mg/5 mg: White to off-white oval, biconvex tablets with 4 I 5 on one side.

PEARLOC 4 mg/10 mg: White to off-white rectangular, biconvex tablets with 4 I 10 on one side.

PEARLOC 8 mg/5 mg: White to off-white triangular, biconvex tablets with 8 I 5 on one side.

PEARLOC 8 mg/10 mg: White to off-white round, biconvex tablets with 8 I 10 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PEARLOC is indicated for the treatment of hypertension in patients already stabilised with perindopril and amlodipine at equivalent dosages.

Treatment of hypertension in patients uncontrolled on either perindopril or amlodipine monotherapy.

4.2 Posology and method of administration

Posology

One tablet per day as a single dose, preferably to be taken in the morning before breakfast.

The fixed dose combination is not suitable for initiation therapy.

If a change in dose is required, the dose of PEARLOC should be modified.

Special populations

Patients with renal impairment and elderly (See section 4.4):

Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium. PEARLOC can be administered in patients with $Cl_{cr} \geq 60$ mL/min and is not suitable for patients with $Cl_{cr} < 60$ mL/min. In these patients, an individual dose titration with the mono-components is recommended.

Normal dosage regimens are recommended in the elderly. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment.

Amlodipine is not dialysable.

Patients with hepatic impairment (See section 4.4 and 5.2):

Dosage recommendations have not been established in patients with mild to moderate hepatic

impairment; therefore, dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). To find the optimal starting dose and maintenance dose of patients with hepatic impairment, the patient should be individually titrated using the free combination of amlodipine and perindopril. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Paediatric population

PEARLOC should not be used in children and adolescents as the efficacy and tolerability of perindopril and amlodipine, in combination, have not been established in children and adolescents.

Method of administration

For oral administration.

4.3 Contraindications

Linked to perindopril:

- hypersensitivity to perindopril
- a history of angioedema related to previous therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines (see section 4.4)
- hereditary or idiopathic angioedema (see section 4.4)
- hypertrophic obstructive cardiomyopathy (HOCM) (see section 4.4)
- severe renal function impairment (creatinine clearance less than 30 ml/min) (see section 4.2 and section 4.4)
- bilateral renal artery stenosis (see section 4.4)
- renal artery stenosis in patients with a single kidney (see section 4.4)
- aortic stenosis (see section 4.4)

- concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance less than 50 ml/min) and in elderly patients (see section 4.4 and section 4.5)
- concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- porphyria
- lithium therapy: Concomitant use with PEARLOC may lead to toxic blood concentration of lithium (see section 4.5)
- pregnancy and lactation (see section 4.4 and section 4.6)
- the concomitant use of PEARLOC with aliskiren-containing products is contraindicated (see section 4.4. and section 4.5)
- concomitant use with sacubitril/valsartan (see sections 4.4 and 4.5). PEARLOC must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan)
- extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).

Linked to amlodipine:

- hypersensitivity to amlodipine or to dihydropyridines derivatives
- 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 with grapefruit juice (see section 4.5).

Linked to PEARLOC:

All contraindications related to each mono-component, as listed above

should apply also to the fixed combination of PEARLOC.

- hypersensitivity to any of the ingredients of PEARLOC (see section 6.1).

4.4 Special warnings and precautions for use

All warnings related to each active ingredient, as listed below, should also apply to the fixed combination of PEARLOC.

Linked to perindopril:

Should a woman become pregnant while taking PEARLOC, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6)

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension hyperkalaemia and decreases renal function (including acute renal failure).

Dual blockade of RAAS through the combined use of PEARLOC and aliskiren is therefore contraindicated (see section 4.3).

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.

PEARLOC and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy (see sections 4.3 and 4.5).

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported in patients treated with ACE-inhibitors including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, PEARLOC 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 (epinephrine) and/or the maintenance of a patient's 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 PEARLOC (see section 4.3).

Intestinal angioedema has been reported in patients treated with ACE-inhibitors such as in PEARLOC. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases, there were 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 PEARLOC 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 mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus, everolimus temsirolimus*), other neprilysin (NEP) inhibitors (e.g. racecadotril):**

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) 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). Caution should be used when starting racecadotril, mTOR inhibitors and gliptins in a patient already taking and ACE-inhibitor.

Concomitant use of fluoroquinolones and ACE inhibitors /Angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/angiotensin receptor blockers, whether used separately and/or concomitantly.

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

Patients receiving perindopril, as in PEARLOC during low-density lipoprotein (LDL) apheresis with dextran sulphate have rarely experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

***Anaphylactic reactions during desensitisation*:**

Patients receiving ACE-inhibitors, such as in PEARLOC, 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 re-challenge.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:

Neutropenia/agranulocytosis/thrombocytopenia/anaemia have been reported in patients receiving ACE-inhibitors such as in PEARLOC. In patients with normal renal function and no other complicating factors, neutropenia rarely occurs.

PEARLOC 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 did not always respond to intensive antibiotic therapy.

If PEARLOC 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).

Hypotension:

ACE-inhibitors may cause a fall in blood pressure. Symptomatic hypotension is rarely seen 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 section 4.5 and section 4.8).

In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with PEARLOC.

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 usually be given without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure, who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with PEARLOC. If hypotension becomes symptomatic, a reduction of the dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:

PEARLOC should be administered with caution to patients with mitral valve stenosis and is contraindicated in patients with obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy (see section 4.3).

Renal impairment:

In cases of renal impairment (creatinine clearance < 60 ml/min) an individual dose titration with the mono-components is recommended (see section 4.2).

Hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function in those patients with symptomatic heart failure. Acute renal failure, usually reversible, has been reported in this situation.

Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).

PEARLOC is contraindicated in patients with bilateral renal artery stenosis, or stenosis of the artery to a solitary kidney due to an increased risk of renal function impairment. In patients treated with PEARLOC, increases in blood urea and serum creatinine may occur.

This is usually reversible upon discontinuation of therapy. It 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.

Dosage reduction and/or discontinuation of the diuretic and/or PEARLOC may be required.

Hepatic failure:

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

Race:

ACE-inhibitors cause a higher rate of angioedema in black patients than in non-black patients. PEARLOC, therefore, 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 commonly with the use of ACE-inhibitors.

Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. PEARLOC induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia:

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, PEARLOC may block angiotensin II formation secondary to compensatory renin release. The treatment 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.

Elevations in serum potassium have been observed in patients treated with PEARLOC.

Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin receptor blockers.

The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal dysrhythmias. (see sections 4.3 and 4.5).

Diabetic patients:

In diabetic patients treated with oral antidiabetic medicines or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE-inhibitor such as in PEARLOC (see section 4.5).

Haemodialysis patients

Anaphylactic 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 medicine (see section 4.5).

Kidney transplantation

There is no experience regarding the administration of PEARLOC in patients with a recent kidney transplant.

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).

Linked to amlodipine:

The safety and efficacy of amlodipine, as in PEARLOC, in hypertensive crisis has not been established

.

Use in patients with cardiac failure:

Patients with heart failure should be treated with caution.

In a long-term, placebo-controlled study in patients with severe heart failure New York heart association functional classification (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.

Use in patients with impaired hepatic function:

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

function; dosage recommendations have not been established. Individual titration with the free combination should be done before the patient is switched back to PEARLOC (fixed dose combination).

Use in elderly patients:

Amlodipine clearance is decreased with resulting increases in AUC (40 – 60 %) and elimination half-life in elderly patients. AUC and elimination half-life in patients with congestive heart failure (CHF) were increased with age.

In the elderly increase of the dosage should take place with care (see section 4.2 and section 5.2).

Use in renal failure:

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

Concomitant use with potent cytochrome CYP3A4 medicines

The blood pressure lowering effect may be enhanced when potent CYP3A4 inhibitors such as ketoconazole, itraconazole or ritonavir are co-administered (see section 4.5).

Linked to PEARLOC:

The concomitant use of PEARLOC with lithium, potassium-sparing diuretics or potassium supplements, or dantrolene is contraindicated. (see sections 4.3 and 4.5).

Excipients with known effect

PEARLOC contains sodium

PEARLOC contains less than 1 mmol sodium (0,023 g) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Linked to perindopril:

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren:

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 (see section 4.3 and section 4.4).

Concomitant use contraindicated (see section 4.3):

Aliskiren:

In diabetic patients or patients with renal impairment, the 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. polyacrylonitrile 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 medicine.

Sacubitril/valsartan:

The concomitant use of perindopril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after taking the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers may

precipitate acute kidney injury (see section 4.3).

The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3 and section 4.4).

Concomitant use not recommended:

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

Although serum potassium remains within the normal limits, hyperkalaemia may occur in some patients taking PEARLOC. ACE-inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics e.g. spironolactone, triamterene or amiloride, potassium supplements or potassium containing salt substitutes may lead to significant increases in serum potassium and are therefore, not recommended (see sections 4.3 and 4.4). If the concomitant use is indicated because of documented hypokalaemia, it should be used cautiously and with frequent monitoring of potassium.

Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker:

Patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with an ACE-inhibitor and an angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system medicine. 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 (see section 4.4).

Lithium:

Reversible increases in serum lithium concentrations and toxicity (severe neurotoxicity) have been reported during concurrent use of ACE-inhibitors. The combination of PEARLOC with lithium is contraindicated (see section 4.3).

Estramustine:

Risk of increased adverse effects such as angioedema.

Co-trimoxazole (trimethoprim/sulfamethoxazole):

Patients taking concomitant co-trimoxazole may be at increased risk for hyperkalaemia.

Concomitant use which requires special care:

***Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥ 3 g/day*:**

When ACE-inhibitors are administered simultaneously with nonsteroidal 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 PEARLOC 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.

Antidiabetic medicines (insulin, hypoglycaemic sulphonamides):

The use of ACE-inhibitors such as PEARLOC may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides.
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 excessive reduction in blood pressure after initiation of therapy with an ACE-inhibitor such as in PEARLOC. 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.

Baclofen:

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

Arterial hypertension:

In arterial 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.

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

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

***Diuretic-treated congestive heart failure*:**

In diuretic-treated congestive heart failure, the ACE-inhibitor, such as in PEARLOC should be initiated at a very low dosage, possibly 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.

Concomitant use to be taken into consideration:

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin):

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

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 PEARLOC. 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 PEARLOC.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of PEARLOC.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold and concomitant ACE-inhibitor therapy like PEARLOC.

Antihypertensive medicines and vasodilators

Concomitant use of these medicines may increase the hypotensive effects of PEARLOC. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Tricyclic antidepressants/antipsychotics/anaesthetics

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE-inhibitors may result in further reduction of blood pressure (see section 4.4).

Linked to amlodipine:

Concomitant use contraindicated:

Grapefruit juice:

Administration of PEARLOC with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects (see

section 4.3).

Concomitant use not recommended:

Dantrolene (infusion):

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

Concomitant use which requires special care:

CYP3A4 inducers:

There is no data available regarding the effect of CYP3A4 inducers on amlodipine, as in PEARLOC. The concomitant use of CYP3A4 inducers (e.g., rifampicin, St John's Wort (*Hypericum perforatum*)), may give a lower plasma concentration of amlodipine. PEARLOC should be used with caution together with CYP3A4 inducers.

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 dose adjustment may thus be required.

***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.

Ciclosporin:

No medicine 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 for 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 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.

Concomitant use to be taken into consideration:

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicines with antihypertensive properties.

Sildenafil:

A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each medicine independently exerted its own blood pressure lowering effect.

Other concomitant use:

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Ethanol:

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

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.

Medicine/laboratory test interactions:

None known.

Linked to PEARLOC:

The above listed interactions apply, as well as the following:

Concomitant use which requires special care:

***Baclofen*:**

Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

Concomitant use to be taken into consideration:

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

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

Corticosteroids, tetracosactide:

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

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

Increased antihypertensive effect and an increased risk of orthostatic hypotension.

Amifostine:

May potentiate the antihypertensive effect of amlodipine contained in PEARLOC.

Tricyclic antidepressants / antipsychotics / anaesthetics:

Increased antihypertensive effect and an increased risk of orthostatic hypotension.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential and their partners should be advised to ensure adequate contraceptive cover.

Pregnancy

Linked to perindopril:

The use of PEARLOC is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take PEARLOC during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety- profile for use in pregnancy.

When pregnancy is diagnosed, treatment with PEARLOC should be stopped immediately and if appropriate, alternative therapy should be started. Foetal exposure to ACE-inhibitors, such as in PEARLOC, during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations.

PEARLOC passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE inhibitors during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Linked to amlodipine:

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

Breastfeeding

Linked to perindopril:

Because no information is available regarding the use of perindopril during lactation, PEARLOC is contraindicated during lactation (see section 4.3).

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, therefore, PEARLOC is contraindicated during lactation (see section 4.3).

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.

4.7 Effects on ability to drive and use machines

No studies on the effects of PEARLOC on the ability to drive and use machines have been performed. Caution is advised as amlodipine can have minor or moderate influence the ability to drive

and use machines. If patients suffer from dizziness, headache, fatigue, weariness or nausea, their ability to react may be impaired.

4.8 Undesirable effects

a. Summary of the safety profile

Perindopril:

The most frequent adverse events reported in clinical trials and observed with perindopril are: dizziness, headache, paraesthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, pruritus, rash, muscle cramps, and asthenia.

Amlodipine

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

The following side effects have been observed during treatment with perindopril or amlodipine given separately:

b. Tabulated list of adverse effects

The frequencies of adverse events are ranked according to the following:

Frequent = common (≥ 1/100 to < 1/10) and very common (≥1/10) .

Less frequent = Infrequent (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000);

Very rare (<1/10 000).

Frequency not known = cannot be estimated from the available data.

Perindopril:

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Rhinitis

Blood and lymphatic system disorders	Less frequent	Eosinophilia, leucopenia / neutropenia, agranulocytosis or pancytopenia, thrombocytopenia, haemolytic anaemia in patients with a congenital deficiency of G-6PDH, haemoglobin decreased, haematocrit decreased
Immune system disorders	Less frequent	Allergic reactions, angioedema of face, extremities, lips, mucous membranes, tongue, glottis, and/or larynx
Endocrine disorders	Less frequent	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia, hyperkalaemia reversible on discontinuation, hyperglycaemia, hyponatraemia
Psychiatric disorders	Less frequent	Mood changes (including anxiety), sleep disturbances, depression

Nervous system disorders	Frequent Less frequent	Dizziness*, headache*, dysgeusia, paraesthesia Somnolence*, syncope, confusional state, cerebrovascular accident (possibly secondary to excessive hypotension in high-risk patients) *Especially at the beginning of the treatment
Eye disorders	Frequent	Visual disturbances
Ear and labyrinth disorders	Frequent	Tinnitus, vertigo
Cardiac disorders	Less frequent	Palpitations, tachycardia, angina pectoris, myocardial infarction (possibly secondary to excessive hypotension in high-risk patients), dysrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation)
Vascular disorders	Less frequent Frequency unknown	Hypotension, vasculitis, flushing, stroke (possibly secondary to excessive hypotension in high-risk patients) Raynaud’s phenomenon

Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Dyspnoea, cough Bronchospasm, eosinophilic pneumonia
Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, constipation Dry mouth, pancreatitis
Hepatobiliary disorders	Less frequent	Hepatitis (cytolytic or cholestatic)
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, rash, exanthema Angioedema (face, mucous membranes, tongue, glottis and/or larynx), hyperhidrosis, urticaria, photosensitivity, pemphigoid, psoriasis aggravation, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Muscle cramps Arthralgia, myalgia
Renal and urinary disorders	Less frequent	Renal impairment, acute renal failure, anuria/oliguria
Reproductive system and breast disorders	Less frequent	Erectile dysfunction (impotence)

General disorders and administrative site conditions	Frequent Less frequent	Asthenia Peripheral oedema, chest pain, malaise, pyrexia
Investigations	Less frequent	Increases in blood urea and serum creatinine, serum bilirubin and liver enzymes elevation, decrease in haemoglobin and haematocrit
Injury and poisoning	Less frequent	Fall

Amlodipine:

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Less frequent	Rhinitis
Blood and lymphatic system disorders	Less frequent	Leucopenia / neutropenia, thrombocytopenia
Immune system disorders	Less frequent	Allergic reactions, angioedema of face, extremities, lips, mucous membranes, tongue, glottis, and/or larynx
Metabolism and nutrition disorders	Less frequent	Hyperglycaemia
Psychiatric disorders	Less frequent	Insomnia, mood changes (including anxiety), depression

Nervous system disorders	Frequent Less frequent Frequency unknown	Somnolence*, dizziness*, headache* *Especially at the beginning of treatment Dysgeusia, tremor, hypoaesthesia, paraesthesia, syncope, confusional state, hypertonia, peripheral neuropathy Extrapyramidal disorder (extrapyramidal syndrome)
Eye disorders	Frequent	Visual disturbances, diplopia
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Frequent Less frequent	Palpitations Dysrhythmia (bradycardia, ventricular tachycardia, atrial fibrillation), myocardial infarction (possibly secondary to excessive hypotension in high-risk patients)
Vascular disorders	Frequent Less frequent	Flushing Hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Dyspnoea Cough

Gastrointestinal disorders	Frequent Less frequent	Abdominal pain, nausea, dyspepsia, altered bowel habits, diarrhoea, constipation Vomiting, dry mouth, pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Less frequent	Hepatitis, jaundice, hepatic enzymes increased
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria, Stevens-Johnson syndrome, exfoliative dermatitis, photosensitivity, Quincke's oedema, angioedema (face mucous membranes, tongue, glottis, and/or larynx), erythema multiforme Toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent	Ankle swelling (joint swelling), muscle cramps Arthralgia, myalgia, back pain
Renal and urinary disorders	Less frequent	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Less frequent	Erectile dysfunction (impotence), gynaecomastia

General disorders and administrative site conditions	Frequent Less frequent	Oedema, fatigue, asthenia Chest pain, pain, malaise
Investigations	Less frequent	Weight increase, weight decrease

c. Description of selected adverse reactions

Additional information linked to perindopril:

Cases of 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.

Additional information linked to amlodipine:

Cases of extrapyramidal syndrome have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

There is no information on overdosage with PEARLOC in humans.

Amlodipine:

Experience with intentional overdose in humans is limited.

Signs and symptoms:

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24 - 48 hours post-ingestion) and require ventilator support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Perindopril:

Limited data are available for overdosage in humans.

Signs and symptoms:

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.

Management of overdose:

Amlodipine:

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.

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.

Perindopril:

The recommended treatment of over dosage is intravenous infusion of 0,9 % sodium chloride 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: ACE inhibitors and calcium channel blockers.

ATC code: C09BB04.

Pharmacological classification: A 7.1.3 Other hypotensives.

Mechanism of action

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*.

Hypertension:

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 75 - 100 % of peak effects.

In responding patients, the maximum antihypertensive effect is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy. In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.

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.

5.2 Pharmacokinetic properties

The rate and extent of absorption of perindopril and amlodipine in combination as in PEARLOC 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.

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 angiotensin converting enzyme but is concentration dependent.

Biotransformation:

Perindopril is a prodrug. Twenty seven percent (27 %) 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 - 4 hours.

Elimination:

Perindopril 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. Dialysis clearance of perindoprilat is equal to 70 mL/min.

Linearity/non-linearity:

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

Pharmacokinetics in special patient groups

Renal impairment and elderly*:*

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2 and section 4.4).

Hepatic impairment*:*

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 section 4.2).

Amlodipine:

Absorption:

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.

Elimination/Biotransformation:

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

Pharmacokinetics in special patient groups

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 (approximately by 40 - 60 %) and elimination half-life in elderly patients.

Use in patients with impaired hepatic function:

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40 - 60 %.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, anhydrous

Cellulose, microcrystalline

Crospovidone

Glycerol dibehenate

Magnesium oxide, light

Magnesium stearate

Sodium starch glycolate (type A)

Trehalose dihydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Pearloc 4 mg/5 mg: 24 months

Pearloc 4 mg/10 mg: 15 months

Pearloc 8 mg/5 mg: 24 months

Pearloc 8 mg/10 mg: 24 months

6.4 Special precautions for storage

Store at or below 25 °C in a cool, dry place.

Store in the original container and protect from light and moisture.

6.5 Nature and contents of container

The tablets are available in aluminium/aluminium blister packs contained in a printed outer carton.

Each carton contains 30 tablets.

The tablets are available in HDPE containers, sealed with foil and a polypropylene (PP)

child resistant cap. Each container contains 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

PEARLOC 4 mg/5 mg: A50/7.1.3/0230

PEARLOC 4 mg/10 mg: A50/7.1.3/0231

PEARLOC 8 mg/5 mg: A50/7.1.3/0232

PEARLOC 8 mg/10 mg: A50/7.1.3/0233

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26 January 2021

10. DATE OF REVISION OF THE TEXT

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