Applicant: Teva Pharmaceuticals (Pty) Ltd
Product name: TEPRILAM 5/5 ; 5/10 ; 10/5 ; 10/10
Dosage form & strength: Each tablet contains 5 mg or 10 mg perindopril tosilate and 5 mg or 10 mg amlodipine, respectively.
Registration Numbers: 55/7.1.3/0809 ; 55/7.1.3/0810 ; 55/7.1.3/0811 ; 55/7.1.3/0812

PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

TEPRILAM 5/5 (tablets)

TEPRILAM 5/10 (tablets)

TEPRILAM 10/5 (tablets)

TEPRILAM 10/10 (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

TEPRILAM 5/5: Each tablet contains 5 mg perindopril tosilate equivalent to 3,6 mg perindopril converted *in situ* to perindopril sodium and 6,935 mg amlodipine besilate equivalent to 5 mg amlodipine.

TEPRILAM 5/10: Each tablet contains 5 mg perindopril tosilate equivalent to 3,6 mg perindopril converted *in situ* to perindopril sodium and 13,87 mg amlodipine besilate equivalent to 10 mg amlodipine.

TEPRILAM 10/5: Each tablet contains 10 mg perindopril tosilate equivalent to 7,2 mg perindopril converted *in situ* to perindopril sodium and 6,935 mg amlodipine besilate equivalent to 5 mg amlodipine.

TEPRILAM 10/10: Each tablet contains 10 mg perindopril tosilate equivalent to 7,2 mg perindopril converted *in situ* to perindopril sodium and 13,87 mg amlodipine besilate equivalent to 10 mg amlodipine.

Excipient with known effect:

Each TEPRILAM 5/5 contains 86,6 mg of isomalt

Each TEPRILAM 5/10 contains 86,6 mg of isomalt

Each TEPRILAM 10/5 contains 173,2 mg of isomalt

Each TEPRILAM 10/10 contains 173,2 mg of isomalt

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Tablets

TEPRILAM 5/5: White, oval, biconvex tablet, debossed 5/5 on one side and plain on the other side. Dimensions: approx. 9 × 5 mm

TEPRILAM 5/10: White, round, biconvex tablet, debossed 5/10 on one side and plain on the other side. Dimension: approx. 7 mm diameter

TEPRILAM 10/5: White, oval, biconvex tablet, debossed 10/5 on one side and plain on the other side. Dimensions: approx. 13 × 7 mm

TEPRILAM 10/10: White, round, biconvex tablet, debossed 10/10 on one side and plain on the other side. Dimension: approx. 9 mm diameter

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

TEPRILAM 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 TEPRILAM 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. TEPRILAM 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 monocomponents 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 **sections 4.4** and **5**)*:

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**). To find the optimal starting dose and maintenance dose of patients with hepatic impairment, the patients 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:

TEPRILAM 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 (ACE inhibitor) or any other ACE-inhibitor
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy. These patients must never again be given these medicines (see **section 4.4**).
- Hereditary/idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Pregnancy and lactation (see **section 4.6**)
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- The concomitant use of TEPRILAM with aliskiren-containing products
- Concomitant use with sacubitril/valsartan (see **sections 4.4** and **4.5**)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see **section 4.5**)
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **section 4.5**)

- Porphyria
- Lithium therapy: Concomitant administration with TEPRILAM may lead to toxic blood concentrations of lithium. (see **section 4.5**)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Concomitant use of fluoroquinolones with ACE-inhibitors/Renin angiotensin receptor blockers is contraindicated in patients with moderate to severe renal failure (creatinine clearance ≤ 30 ml/min) and in elderly patients.

Linked to amlodipine:

- Hypersensitivity to amlodipine or to any other dihydropyridine 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.

Linked to TEPRILAM:

- Hypersensitivity to any of the excipients listed in **section 6.1**
- All contraindications related to each mono-component, as listed above, should also apply to the fixed combination of perindopril and amlodipine.

4.4 Special warnings and precautions for use:

All warnings related to each mono-component, as listed below, should apply also to the fixed combination of perindopril and amlodipine.

***Linked to perindopril*:**

Should a woman become pregnant while receiving TEPRILAM, 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 TEPRILAM and aliskiren is therefore contraindicated (see **section 4.3**).

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

Aliskiren:

TEPRILAM should not be used concomitantly with aliskiren. (see **section 4.3**).

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, TEPRILAM 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 epinephrine

(adrenaline) 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 TEPRILAM (see **section 4.3**).

Intestinal angioedema has been reported 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**).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of perindopril. Treatment with perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see **sections 4.3** and **4.5**). Concomitant use of other NEP inhibitors (e.g racecadotril) with an ACE inhibitor may also increase the risk of angiodema (see **section 4.5**). Therefore, a careful assessment of the benefit to risk ratio is necessary before initiating a treatment with NEP inhibitors (e.g. racecadotril) in patients receiving perindopril.

Concomitant use of ACE inhibitors with mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) or 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 mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) or vildagliptin in a patient already taking an ACE inhibitor.

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

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 resumption of treatment.

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. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever) (see **sections 4.5** and **4.8**).

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see **section 4.3**). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Primary hyperaldosteronism:

Patients with primary hyperaldosteronism do not generally respond to antihypertensive medicines which work by inhibiting the renin-angiotensin system. As a result, the use of this medicine is not recommended in these patients.

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. 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 (see **sections 4.3** and **4.6**).

Precautions for use:

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 the combination of perindopril and amlodipine.

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 isotonic sodium chloride. Transient hypotension 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 such as perindopril contained in TEPRILAM should be given with caution to patients with mitral valve stenosis and is contraindicated in 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 monocomponents is recommended (see **section 4.2**).

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

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

Race:

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril 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:

A dry cough has been reported with the use of ACE inhibitors. 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, the combination of perindopril and amlodipine 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.

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, inter-current 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, cotrimoxazole 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.

Hyperkalaemia can cause serious, sometimes fatal dysrhythmias. If concomitant use of perindopril and any of the above mentioned medicines is deemed appropriate, because of documented hypokalaemia, 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 medicines or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see **section 4.5**).

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE-inhibitors/renin 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/renin angiotensin receptor blockers whether used separately or concomitantly.

Linked to amlodipine:

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.

In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see **section 5.1**). 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.

Hepatic impairment:

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly:

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

Renal impairment:

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

Amlodipine is not dialysable.

Linked to the combination of perindopril and amlodipine:

All warnings related to each mono-component, as listed above, should apply also to the fixed combination of perindopril and amlodipine.

Precautions for use:

Interactions:

The concomitant use of the combination of TEPRILAM with lithium, potassium-sparing diuretics or potassium supplements, or dantrolene is contraindicated (see **section 4.5**).

Excipient(s):

Level of sodium:

TEPRILAM contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'.

Isomalt:

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction:

Linked to perindopril:

Clinical trial data shows that, compared to a single agent acting on RAAS, double depression of the renin-angiotensin-aldosterone system (RAAS) with ACE combination of inhibitors, angiotension II receptor blockers, or aliskiren, associated with more common adverse events such as hypotension, hyperkalaemia and renal impairment (including acute renal failure) (see **sections 4.3, 4.4** and **5.1**).

Medicines that cause hyperkalaemia:

Some medications or some classes of medications may increase hyperkalaemia risk, for example, aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor blockers, NSAIDs, heparins, immunosuppressant’s (e.g. ciclosporin or tacrolimus), tripmethoprim and fixed dose combination with sulfamethoxazole (co-trimoxazole). The concomitant use of medicines increases the risk of hyperkalaemia.

Concomitant use contraindicated:

Aliskiren:

In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Extracorporeal circulation treatment:

Extracorporeal treatment that causes blood to interact with negatively charged surfaces, for example, using high-permeability membranes during dialysis or haemofiltration (e.g. polyacrylonitrile membranes) or low density lipoprotein apheresis with dextran sulfate may increase the risk of severe anaphylactoid reactions (see **section 4.3**). If such treatment is needed, it is necessary to use a different type of dialysis membrane or prescribe another class of antihypertensive medicine.

Sacubitril/Valsartan:

Perindopril should not be administered concomitantly with sacubitril/valsartan as the concommitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan should not be initiated until 36 hours after the last dose of perindopril. Perindopril treatment is contraindicated within 36 hours of the last dose of sacubitil/valsartan (see **sections 4.3** and **4.4**).

Lithium:

TEPRILAM is contraindicated in patients on lithium therapy (see **section 4.3**). An increase in lithium levels may occur.

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE-inhibitors/renin 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/renin angiotensin receptor blockers whether used separately or concomitantly.

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

Hyperkalaemia (potentially life-threatening), particularly in a context of renal failure (cumulative hyperkalaemic medicines). The combination of perindopril with the medicines mentioned above is contraindicated (see **section 4.3**). If concomitant use is indicated, however, these medicines should be used with caution and periodic monitoring of serum potassium should be performed. For the use of the spironolactone in heart failure, see below.

Concomitant use not recommended:

Concomitant use with ACE inhibitors and angiotensin receptor blockers:

There are reports in the literature that in patients with atherosclerotic disease, heart failure, or diabetes mellitus with end-stage organ failure, concomitant therapy with an ACE inhibitor and angiotensin receptor blocker is associated with hypotension, hyperkalaemia and increased renal impairment (including acute renal failure) compared to single renin-angiotensin-aldosterone system agent.

Estramustine:

Risk of increased adverse effects such as angioedema.

Co-trimoxazole (trimethoprim/sulfamethaoxazole):

Patients receiving co-trimoxazole (trimethoprim/sulfamethoxazole) may be at risk of hyperkalaemia (see **section 4.4**).

Concomitant use which requires special care:

Antidiabetic medicines (insulin, hypoglycaemic sulphonamides):

The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (there is probably an improvement in glucose tolerance with a resulting reduction in insulin requirements).

Non-potassium-sparing diuretics:

The initiation of treatment with an ACE inhibitor may lead to an excessive reduction in blood pressure in patients taking diuretics, especially those who lack fluid and or electrolytes in the body . The reductive risk of hypotensive effects is possible with discontinuation of diuretics, increased intake of fluids or salts before starting treatment with low, progressively increasing doses of perindopril.

In treatment of patients with arterial hypertension who have had previous diuretic therapy there may have been a reduction in the amount of electrolytes or fluids in the body, or the need to discontinue diuretics before starting ACE inhibitors (in which case potassium may be reintroduced later, non-adherent diuretics), or a low dose ACE inhibitor, possibly followed by a low dose with progressive increments.

In diuretic-treated patients with congestive heart failure, at the start of treatment, use a very low dose of an ACE inhibitor, possibly following a previous non-potassium related retention dose reduction of the diuretic. In all cases, renal function (creatinine concentrations) should be monitored during the first few weeks of treatment with an ACE inhibitor.

Potassium sparing diuretics (eplerenone, spironolactone):

Eplerenone or spironolactone (12,5 mg to 50 mg doses) with low ACE inhibitor doses in patients with class II-IV heart failure (NYHA) and with an ejection fraction of less than 40 %, previously treated with ACE

inhibitors and loop diuretics, the risk of hyperkalaemia, which can be fatal, especially if the combination is not prescribed. Before initiating therapy with this combination, it is necessary to make sure that there is no hyperkalaemia and no kidney dysfunction. Initially (during the first month of treatment) careful monitoring of potassium and sodium is recommended to check creatinine blood levels once a week and then monthly measurements.

Racecadotril:

ACE inhibitors (such as perindopril) are known to cause angioedema. This risk may be higher with racecadotril (a medicine used to stop diarrhoea).

mTOR inhibitors (eg sirolimus, everolimus, temsirolimus):

Patients receiving concomitant treatment with mTOR inhibitors may be at increased risk of angioedema (see **section 4.4**).

Non-steroidal anti-inflammatory medicines (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 ACE-inhibitors 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.

Concomitant use to be taken into consideration:

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin):

Patients at increased risk of angioedema due to decreased activity in the dipeptidyl peptidase IV (DPP-IV) caused by gliptins in patients co-treated with ACE inhibitors.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Linked to amlodipine:

Concomitant use not recommended:

Dantrolene (infusion):

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

Concomitant use which requires special care:

CYP3A4 inducers:

When co-administering known inducers of 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 potent CYP3A4 inducers (e.g. rifampicin, St. John's wort

[*hypericum perforatum*]).

CYP3A4 inhibitors:

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Therefore clinical monitoring and dose adjustment may be required.

There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

Concomitant use to be taken into consideration:

The hypotensive effects of amlodipine are additional to those of other medicines with antihypertensive properties.

Tacrolimus:

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

mTOR (Mechanistic Target of Rapamycin) Inhibitors:

Inhibitors of mTOR such as sirolimus, temsirolimus and everolimus are CYP3A substrates. Since amlodipine is a weak inhibitor of CYP3A, it may increase exposure to mTOR inhibitors when used concomitantly.

Ciclosporin:

No interaction studies were conducted with ciclosporin and amlodipine in healthy volunteers or other populations, with the exception of patients who have had a kidney transplant, with varying increase in the minimum concentration of ciclosporin (from 0 % to 40 % on average). Ciclosporin blood levels should be monitored in subjects who have had a renal transplant and who are receiving amlodipine and a reduction in the dose of ciclosporin should be considered if needed.

Simvastatin:

Co-administration of repeated doses of 10 mg amlodipine with 80 mg simvastatin results in a 77 % increase in simvastatin exposure with simvastatin alone. The daily dose of simvastatin should be limited to 20 mg in patients treated with amlodipine.

Other combinations:

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

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

Linked to the combination of perindopril and amlodipine:

Concomitant use which requires special care:

Baclofen:

Increased antihypertensive effect. If necessary, monitor the blood pressure and adjust the dosage of the antihypertensive.

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 perindopril and amlodipine.

Concomitant use with nitroglycerin and 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 increased risk of orthostatic hypotension.

Amifostine:

May potentiate the antihypertensive effect of amlodipine.

Tricyclic antidepressants/antipsychotics/anaesthetics:

Increased antihypertensive effect and increased risk of orthostatic hypotension.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Linked to perindopril:

The use of TEPRILAM is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take TEPRILAM 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 TEPRILAM should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors 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 spins bifida) and of kidney malformations.

TEPRILAM 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 TEPRILAM 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 (see **section 5.3**).

Breastfeeding:

Linked to perindopril:

Because no information is available regarding the use of perindopril during lactation, perindopril is contraindicated.

Linked to amlodipine:

Safety of amlodipine during ·lactation has not been established. It is not known whether amlodipine is excreted in breast milk.

Fertility:

Linked to perindopril:

There was no effect on reproductive function 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 the combination of perindopril and amlodipine on the ability to drive and use machines have been performed.

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients treated with amlodipine experience dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects:

Summary of the safety profile:

The most common side effects reported with perindopril and amlodipine use are: oedema, drowsiness, dizziness, headache (especially at the beginning of treatment), dysgeusia, paresthesia, visual defects (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnoea, cough, abdominal pain, nausea, vomiting, dyspepsia, intestinal transit, diarrhoea, constipation,

pruritis, rash, exanthema, swelling of the joint (swelling of the ankles), contractures muscle, fatigue and asthenia.

Tabulated list of adverse reactions:

MedDRA System Organ Class	**Description**	**Frequency**	
		Amlodipine	**Perindopril**
Infections and infestations:	Rhinitis	*Less frequent*	*Less frequent*
Blood and lymphatic system disorders:	Eosinophilia	**--**	*Less frequent**
	Leukopenia/neutropenia (see **section 4.4**)	*Less frequent*	*Less frequent*
	Agranulocytosis or pancytopenia (see **section 4.4**)	--	*Less frequent*
	Thrombocytopenia (see **section 4.4**)	*Less frequent*	*Less frequent*
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see **section 4.4**)	**--**	*Less frequent*
Immune system disorders:	Allergic reactions: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx	*Less frequent*	*Less frequent*

Metabolism and nutrition disorders:	Hyperglycaemia	*Less frequent*	--
	Hypoglycaemia (see **sections 4.4** and **4.5**)	--	*Less frequent**
	Hyperkalaemia, reversible on discontinuation (see **section 4.4**)	--	*Less frequent**
	Hyponatraemia		*Less frequent**
Psychiatric disorders:	Insomnia	*Less frequent*	-
	Mood changes (including anxiety)	*Less frequent*	*Less frequent*
	Depression	*Less frequent*	-
	Sleep disturbances	--	*Less frequent*
Nervous system disorders:	Somnolence (especially at the beginning of the treatment)	*Frequent*	*Less frequent**
	Dizziness (especially at the beginning of the treatment)	*Frequent*	*Frequent*
	Headache (especially at the beginning of the treatment)	*Frequent*	*Frequent*
	Dysgeusia	*Less frequent*	*Frequent*
	Tremor	*Less frequent*	--
	Hypoesthesia Paraesthesia	*Less frequent* *Less frequent*	-- *Frequent*

	Confusional state	*Less frequent*	*Less frequent*
	Syncope	*Less frequent*	*Less frequent**
	Hypertonia	*Less frequent*	--
	Peripheral neuropathy	*Less frequent*	--
	Extrapyramidal disorder	*Not known*	--
	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see **section 4.4**)	--	*Less frequent*
Eye disorders:	Visual disturbances (including diplopia)	*Frequent*	*Frequent*
Ear and labyrinth disorders:	Tinnitus	*Less frequent*	*Frequent*
	Vertigo	--	*Frequent*
Cardiac disorders:	Palpitations	*Frequent*	*Less frequent**
	Angina pectoris (see **section 4.4**)	--	*Less frequent*
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see **section 4.4**)	*Less frequent*	*Less frequent*
	Dysrhythmia (including bradycardia, ventricular	*Less frequent*	*Less frequent*

	tachycardia and atrial fibrillation)		
	Tachycardia	-	*Less frequent**
	Flushing	*Frequent*	--
Vascular disorders:	Hypotension (and effects related to hypotension) (see **section 4.4**)	*Less frequent*	*Frequent*
	Vasculitis	*Less frequent*	*Less frequent**
	Raynaud's phenomenon	--	*Not known*
Respiratory, thoracic and mediastinal disorders:	Cough	*Less frequent*	*Frequent*
	Dyspnoea	*Frequent*	*Frequent*
	Bronchospasm	--	*Less frequent*
	Eosinophilic pneumonia	--	*Less frequent*
Gastrointestinal disorders:	Gingival hyperplasia	*Less frequent*	--
	Abdominal pain	*Frequent*	*Frequent*
	Nausea	*Frequent*	*Frequent*
	Vomiting	*Less frequent*	*Frequent*
	Dyspepsia	*Frequent*	*Frequent*
	Altered bowel habits	*Frequent*	--
	Dry mouth	*Less frequent*	*Less frequent*
	Diarrhoea	*Frequent*	*Frequent*
	Constipation	*Frequent*	*Frequent*
	Pancreatitis	*Less frequent*	*Less frequent*
	Gastritis	*Less frequent*	--

Hepato-biliary disorders:	Hepatitis, cholestatic jaundice Hepatitis either cytolytic or cholestatic (see **section 4.4**)	*Less frequent* --	-- *Less frequent*
	Hepatic enzymes increased (mostly consistent with cholestasis)	*Less frequent*	--
Skin and subcutaneous tissue disorders:	Quincke's oedema Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see **section 4.4**)	*Less frequent* *Less frequent*	-- *Less frequent*
	Erythema multiform	*Less frequent*	*Less frequent*
	Alopecia	*Less frequent*	--
	Purpura	*Less frequent*	--
	Skin discoloration	*Less frequent*	*Less frequent*
	Hyperhidrosis	*Less frequent*	*Less frequent*
	Pruritus	*Less frequent*	*Frequent*
	Rash, exanthema	*Less frequent*	*Frequent*
	Urticaria (see **section 4.4**)	*Less frequent*	*Less frequent*
	Stevens Johnson syndrome	*Less frequent*	--

	Toxic epidermal necrolysis	*Not known*	--
	Exfoliative dermatitis	*Less frequent*	--
	Photosensitivity reaction	*Less frequent*	*Less frequent**
	Psoriasis aggravation	--	*Less frequent*
	Pemphigoid	--	*Less frequent**
Musculoskeletal and connective tissue disorders:	Joint swelling (ankle swelling)	*Frequent*	--
	Arthralgia	*Less frequent*	*Less frequent**
	Myalgia	*Less frequent*	*Less frequent**
	Muscle spasms	*Frequent*	*Frequent*
	Back pain	*Less frequent*	--
Renal and urinary disorders:	Micturition disorder, nocturia, pollakiuria	*Less frequent*	-
	Renal failure	--	*Less frequent*
	Acute renal failure	--	*Less frequent*
Reproductive system and breast disorders:	Gynaecomastia	*Less frequent*	--
	Erectile dysfunction	*Less frequent*	*Less frequent*
General disorders and administration site conditions:	Oedema	*Frequent*	--
	Peripheral oedema	--	*Less frequent*
	Fatigue	*Frequent*	--
	Chest pain	*Less frequent*	*Less frequent**
	Asthenia	*Frequent*	*Frequent*

	Pain	*Less frequent*	-
	Malaise	*Less frequent*	*Less frequent**
	Pyrexia	--	*Less frequent**
Investigations:	Weight increase, weight decrease	*Less frequent*	--
	Serum bilirubin and liver enzymes elevation	--	*Less frequent*
	Increases in blood urea and serum creatinine (see **section 4.4**)	--	*Less frequent**
	Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)	*Less frequent*	--
	Decreased haemoglobin and haematocrit decreased	--	*Less frequent*
Injury, poisoning and procedural complications:	Fall	--	*Less frequent**

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

Additional information:

Exceptional cases of extrapyramidal syndrome have been reported with calcium channel blockers.

Cases of inappropriate secretion of antidiuretic hormone (SIADH) have been reported with other ACE inhibitors. SIADH may be considered a very rare complication but possible treatments include ACE inhibitors, including perindopril.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose:

There is no information on overdosing with the combination of perindopril and amlodipine in humans.

For amlodipine, experience with intentional overdose in humans is limited.

Symptoms: available data suggest that a significant overdose could result in excessive peripheral vasodilation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

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

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

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 overdose 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:

A 7.1.3 Other hypotensives.

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

Perindopril:

Mechanism of action:

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*.

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.

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 from TEPRILAM 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 pro-drug. 27 % of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields 5 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 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.

Elimination:

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Linearity/non-linearity:

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

Special populations:

Elderly:

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure.

Renal impairment:

Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

Hepatic impairment:

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**).

Amlodipine:

Absorption, distribution, plasma protein binding:

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 to 12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. The volume of distribution is approximately 21 litre/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 to 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.

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 40 to 60 %) and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Hepatic impairment:

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

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Cellulose, microcrystalline (type 102)

Isomalt

Magnesium stearate

Povidone K30

Sodium hydrogen carbonate (as starting material)

Sodium starch glycolate (type A)

Water, purified

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

30 months

6.4 Special precautions for storage:

Store at or below 25 °C.

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

6.5 Nature and contents of container:

White opaque polypropylene tablet containers with white opaque polyethylene stopper with desiccant insert equipped with a tamper-evident (TE) polyethylene flow reducer.

Pack sizes of:

TEPRILAM 5/5: 10, 30, 90 (30 x 3) tablets

TEPRILAM 5/10, 10/5, 10/10: 30, 90 (30 x 3) tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand, Gauteng, South Africa

2090

8. REGISTRATION NUMBER:

TEPRILAM 5/5: 55/7.1.3/0809

TEPRILAM 5/10: 55/7.1.3/0810

TEPRILAM 10/5: 55/7.1.3/0811

TEPRILAM 10/10: 55/7.1.3/0812

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

03 October 2023

10. DATE OF REVISION OF THE TEXT: