Applicant: Teva Pharmaceuticals (Pty) Ltd.	**Product name: TREXEVA PLUS 2,5 / 0,625** **TREXEVA PLUS 5 / 1,25**
Registration No.: 48/7.1.3/1168-9	**Dosage Form:** Each film-coated tablet contains 2,5 mg or 5 mg perindopril tosilate and 0,625 mg or 1,25 mg indapamide, respectively

PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE:

TREXEVA PLUS 2,5/0,625 film-coated tablets

TREXEVA PLUS 5/1,25 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

TREXEVA PLUS 2,5/0,625 contains 2,5 mg perindopril tosilate and 0,625 mg indapamide per film-coated tablet.

TREXEVA PLUS 5/1,25 contains 5 mg perindopril tosilate and 1,25 mg indapamide per film-coated tablet.

Excipient with known effect:

TREXEVA PLUS 2,5/0,625 and TREXEVA PLUS 5/1,25 contains sugar (lactose monohydrate 74,056 mg and 148,112 mg per film-coated tablet respectively).

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

3. PHARMACEUTICAL FORM:

Film-coated tablets.

TREXEVA PLUS 2,5/0,625: White, capsule shaped biconvex film-coated tablet of approx. 4 mm width and 8 mm length, debossed breakline on one side and plain on the other side.

TREXEVA PLUS 5/1,25: White, capsule shaped biconvex film-coated tablet of approx. 5 mm width and 10 mm length, debossed “P”, “I” and breakline on one side and plain on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

TREXEVA PLUS is indicated for the treatment of essential hypertension, in patients where blood pressure is not adequately controlled and where fixed combination is considered more appropriate than monotherapy.

4.2 Posology and method of administration:

Posology:

The dosage regimen depends upon the individual requirements of the patient and is at the discretion of the medical practitioner.

One TREXEVA PLUS per day as a single dose, preferably to be taken in the morning before a meal.

Special populations:

Elderly:

It is recommended to start the treatment with only one of the constituents (see **section 4.4**).

Patients with renal failure:

In cases of severe renal failure (creatinine clearance below 30 mL/min), treatment is contraindicated. In patients with a creatinine clearance greater than or equal to 30 mL/min and less than 60 mL/min, it is recommended to start the treatment with only one of the constituents. It is not necessary to change the dose when the creatinine clearance is greater than 60 mL/min (see **section 4.4**).

Method of administration:

For oral use.

4.3 Contraindications:

Linked to perindopril:

- Hypersensitivity to perindopril (ACE inhibitor) or any other excipients (see **section 6.1**)
- 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 impairment (creatinine clearance less than 30 mL/min)
- The concomitant use of TREXEVA PLUS with aliskiren-containing medicines in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m²) (see **sections 4.5** and **5.1**)
- Concomitant use with sacubitril/valsartan. TREXEVA PLUS must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see **sections 4.4** and **4.5**)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see **section 4.5**)
- Severe hepatic impairment
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride. (see **section 4.5**)
- Porphyria
- Lithium therapy: Concomitant administration with TREXEVA PLUS may lead to toxic blood concentrations of lithium. (see **section 4.5**)
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see **section 4.4**)
- 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 indapamide:

- Hypersensitivity to indapamide or to any other sulfonamides
- Severe renal impairment (creatinine clearance below 30 mL/min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- As a general rule, this medicine is inadvisable in combination with non-anti-dysrhythmic medicines causing torsades de pointes (see **section 4.5**)
- Lactation (see **section 4.6**).

Linked to TREXEVA PLUS:

- Hypersensitivity to any of the excipients listed in **section 6.1**
- Dialysis patients
- Patients with untreated decompensated cardiac failure.

4.4 Special warnings and precautions for use:

Special warnings:

Linked to perindopril:

Should a woman become pregnant while receiving TREXEVA PLUS, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (See **sections 4.3** and **4.6**).

Common to perindopril and indapamide:

Lithium:

The combination of lithium and the combination of perindopril and indapamide is contraindicated (see **section 4.3**).

Linked to perindopril:

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 TREXEVA PLUS and angiotensin II receptor blockers or aliskiren is therefore contraindicated (see **sections 4.3, 4.5** and **5.1**). TREXEVA PLUS should not be used concomitantly with aliskiren. (see **section 4.3**).

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

Aliskiren:

Perindopril as contained in TREXEVA PLUS should not be used concomitantly with aliskiren. (see **section 4.3**).

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

The combination of perindopril, as contained in TREXEVA PLUS, and potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes is contraindicated (see **sections 4.3** and **4.5**).

Neutropenia/agranulocytosis/thrombocytopenia/anaemia:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs less frequently. 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.

Hypersensitivity/angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including perindopril (see **section 4.8**). This may occur at any time during treatment. In such cases perindopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine (adrenaline) solution 1:1000 (0,3 mL to 0,5 mL) and/or measures to ensure a patent airway, should be administered promptly. The prescribing of TREXEVA PLUS or any other ACE-inhibitor is then contraindicated in these patients (see **section 4.3**).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (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.

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

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin):

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 (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor, as contained in TREXEVA PLUS.

Anaphylactoid reactions during desensitisation:

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

Anaphylactoid reactions during 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.

Haemodialysis patients:

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

Primary aldosteronism:

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

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 indapamide:

Hepatic encephalopathy:

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of TREXEVA PLUS should be stopped immediately if this occurs.

Photosensitivity:

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

Precautions for use:

Common to perindopril and indapamide:

Renal impairment:

In cases of severe renal impairment (creatinine clearance < 30 mL/min), treatment is contraindicated.

In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only.

In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

TREXEVA PLUS is contraindicated in case of bilateral renal artery stenosis or a single functioning kidney (see **section 4.3**).

Hypotension and water and electrolyte depletion:

There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting. Regular monitoring of plasma electrolytes should be carried out in such patients.

Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.

Transient hypotension is not a contraindication to continuation of treatment.

After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.

Potassium levels:

The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive medicine in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Linked to perindopril:

Cough:

A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the

event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc.):

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.

The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset.

In such cases, the treatment should then be initiated with only one of the constituents and increased progressively.

Elderly:

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

Patients with known atherosclerosis:

The risk of hypotension exists in all patients but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started with only one of the constituents.

Renovascular hypertension:

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

If TREXEVA PLUS is prescribed to patients with known or suspected renal artery stenosis, treatment should be started in a hospital setting with only one of the constituents and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

Cardiac failure/severe cardiac insufficiency

In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with only one of the constituents. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

Diabetic patients

In patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose.

The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic medicines or insulin, namely during the first month of treatment with an ACE inhibitor.

Ethnic differences:

Perindopril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Surgery / anaesthesia:

Angiotensin converting enzyme inhibitors as contained in TREXEVA PLUS can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is a medicine with hypotensive potential.

It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible one day before surgery.

Aortic or mitral valve stenosis / hypertrophic cardiomyopathy:

ACE inhibitors such as perindopril should be used with caution in patients with an obstruction in the outflow tract of the left ventricle.

Hepatic failure:

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

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril.

ACE inhibitors as contained in TREXEVA PLUS can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function.

Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride),

potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole, other ACE-inhibitors, angiotensin-II receptor antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAID's, immunosuppressant medicines such as ciclosporin or tacrolimus, trimethoprim). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal dysrhythmias.

If concomitant use of the abovementioned medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see **section 4.5**).

Linked to indapamide:

Water and electrolyte balance

Indapamide may cause electrolyte imbalances.

Sodium levels:

These should be tested before treatment is started, then at regular intervals.

All diuretic treatment can cause a reduction in sodium levels (hyponatremia), which may have serious consequences.

Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see **sections 4.8** and **4.9**).

Hyponatraemia with hypovolaemia may be responsible for dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.

Potassium levels:

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of lowered potassium levels (< 3,4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medicines, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders.

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required.
Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

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

Plasma magnesium:

Thiazides and related diuretics including indapamide, contained in TREXEVA PLUS, have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see **sections 4.5** and **4.8**)

Blood glucose:

Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

Uric acid:

Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics:

Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockroft formula:

cl_{cr} = (140 - age) x body weight / 0,814 x plasma creatinine level

with:

age expressed in years

body weight in kg

plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0,85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional

renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

Athletes:

Athletes should note that TREXEVA PLUS contains an active substance which may cause a positive reaction in doping tests.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide, or sulfonamide derivative, medicines can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicine initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue medicine intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

TREXEVA PLUS contains sugar (lactose monohydrate):

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TREXEVA PLUS.

Level of sodium:

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

Paediatric population:

Linked to perindopril:

The efficacy and tolerability of perindopril in children and adolescents, alone or in combination, have not been established.

4.5 Interaction with other medicines and other forms of interaction:

Linked to perindopril and indapamide:

Concomitant use contraindicated:

Lithium: TREXEVA PLUS is contraindicated in patients on lithium therapy (see **section 4.3**). Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, as contained in TREXEVA PLUS.

If the combination of an ACE-inhibitor and a potassium-sparing diuretic is unavoidable, strict monitoring of lithium levels and adjustment of the dose are necessary.

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.
- *Non-steroidal anti-inflammatory drugs (included acetylsalicylic acid at high doses):* 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 which requires some care:

- *Imipramine-like antidepressants (tricyclics), neuroleptics*: Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Linked to perindopril:

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

Medicines increasing the risk of angioedema:

Racecadotril: ACE inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a medicine used against acute diarrhoea).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus): patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see **section 4.4**).

Gliptins (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.

Medicines inducing hyperkalaemia:

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with TREXEVA PLUS.

Some medicines or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE inhibitors, angiotensin-II receptor antagonists, NSAIDs, heparins, immunosuppressant medicines such as ciclosporin or tacrolimus, trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride (see **section 4.4**). The combination of these medicines increases the risk of hyperkalaemia. Therefore, the combination of TREXEVA PLUS with the above-mentioned medicines is not recommended.

Concomitant use contraindicated:

- *Aliskiren:* In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.
- *Extracorporeal treatments:* Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile membranes) and low density lipoprotein apheresis with dextran sulfate 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 taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see **sections 4.3** and **4.4**).
- *Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers:* Concomitant use of fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see **section 4.3**).

Concomitant use not recommended:

- *Aliskiren:* In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase (see **section 4.4**).
- *Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker:* It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with 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**).

- *Estramustine:* Risk of increased adverse effects such as angioneurotic oedema (angioedema).
- *Potassium-sparing diuretics (e.g. triamterene, amiloride, potassium salts):* Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of perindopril with the above-mentioned medicines is not recommended (see **section 4.4**). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see section **Concomitant use which requires special care**.

Concomitant use which requires special care:

- *Antidiabetic medicines (insulin, oral hypoglycaemic medicines):* Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic medicines) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

- *Non-potassium-sparing diuretics*: Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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.

In diuretic-treated congestive heart failure, the ACE inhibitor 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.

- *Potassium-sparing diuretics (eplerenone, spironolactone):* With eplerenone or spironolactone at doses between 12,5 mg to 50 mg per day and with low doses of ACE inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 %, and previously treated with ACE inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations about this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

Close monitoring of the kalaemia and creatininaemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Concomitant use which requires some care:

- *Antihypertensive medicines and vasodilatators*: Concomitant use of these medicines may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilatators, may further reduce blood pressure.
- *Allopurinol, cytostatic or immunosuppressive medicines, systemic corticosteroids or procainamide:* Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.
- *Anaesthetic medicine*: ACE inhibitors may enhance the hypotensive effects of certain anaesthetic medicines (see **section 4.4**).
- *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 indapamide:

Concomitant use which requires special care:

- *Torsades de pointes inducing medicines:* Due to the risk of hypokalemia, indapamide should be administered with caution when associated with medicines that induced torsades de pointes such as but not limited to: class IA anti-dysrhythmic medicines (quinidine, hydroquinidine, disopyramide); class III anti-dysrhythmic medicines (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some antipsychotics - phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, sultopride, tiapride), butyrophenones (droperidol, haloperidol), other antipsychotics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine.

Prevention of low potassium levels and correction if necessary; monitoring of the QT interval.

- *Potassium-lowering medicines:* amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives: Increased risk of low potassium levels (additive effect). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides (digitalis). Non stimulant laxatives should be used.
- *Cardiac glycosides (digitalis preparations):* Low potassium levels (hypokalaemia) and/or low magnesium levels (hypomagnesaemia) favour the toxic effects of cardiac glycosides (digitalis). Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjusting the treatment.
- *Allopurinol:* concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Concomitant use which requires some care:

- *Potassium-sparing diuretics (amiloride, spironolactone, triamterene):* Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia (particularly in patients with renal failure or diabetes) may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.
- *Metformin:* Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed 15 mg/l (135 micromol/l)

in men and 12 mg/l (110 micromol/l) in women.

- *Iodinated contrast media:* In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.
- *Calcium (salts):* Risk of increased levels of calcium due to reduced elimination of calcium in the urine.
- *Ciclosporin, tacrolimus:* Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.
- *Corticosteroids, tetracosactide (systemic route):* Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

4.6 Fertility, pregnancy and lactation:

Pregnancy:

The use of TREXEVA PLUS is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take TREXEVA PLUS 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 TREXEVA PLUS 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.

TREXEVA PLUS 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 new-borns, have been reported after administration of TREXEVA PLUS 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**).

Should exposure to ACE-inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken ACE-inhibitors should be closely observed for hypotension (see **section 4.3**).

Breastfeeding:

The use of TREXEVA PLUS is contraindicated during lactation (see **section 4.3**).

Fertility:

Effects on fertility by perindopril or indapamide in humans are not known.

4.7 Effects on ability to drive and use machines:

The two active substances, individually or combined in TREXEVA PLUS, have no influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects:

Summary of the safety profile:

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide.

The most frequently reported adverse reactions observed are:

- with perindopril: dizziness, headache, paraesthesia, dysgeusia, visual impairment, vertigo, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, dyspepsia, diarrhoea, nausea, vomiting, pruritus, rash, muscle cramps and asthenia.
- with indapamide: hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculo-papular rashes.

Tabulated list of adverse reactions:

MedDRA SOC	**Description**	**Frequency**	
		Perindopril	**Indapamide**
Infections and infestations	Rhinitis	*Less frequent*	-
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	*Less frequent*	
Blood and the lymphatic system disorders	Eosinophilia	*Less frequent**	-
	Agranulocytosis (see **section 4.4**)	*Less frequent*	*Less frequent*
	Aplastic anaemia		*Less frequent*
	Pancytopenia	*Less frequent*	-
	Leukopenia	*Less frequent*	*Less frequent*
	Neutropenia (see **section 4.4**)	*Less frequent*	-
	Haemolytic anaemia	*Less frequent*	*Less frequent*

	Thrombocytopenia (see **section 4.4**)	*Less frequent*	*Less frequent*
Immune system disorders	Hypersensitivity (reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions)	-	*Frequent*
Metabolism and nutrition disorders	Hypoglycaemia (see **sections 4.4 and 4.5**)	*Less frequent**	-
	Hyperkalaemia, reversible on discontinuation (see **section 4.4**)	*Less frequent**	-
	Hyponatraemia (see **section 4.4**)	*Less frequent**	*Less frequent*
	Hypochloraemia	-	*Less frequent*
	Hypomagnesaemia	-	*Less frequent*
	Hypercalcaemia	-	*Less frequent*
	Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see **section 4.4**)	-	*Frequent*
Psychiatric disorders	Depression	*Less frequent**	-
	Mood altered	*Less frequent*	-
	Sleep disorder	*Less frequent*	-
	Confusion	*Less frequent*	-

Nervous system disorders	Dizziness	*Frequent*	-
	Headache	*Frequent*	*Less frequent*
	Paraesthesia	*Frequent*	*Less frequent*
	Dysgeusia	*Frequent*	-
	Somnolence	*Less frequent**	-
	Syncope	*Less frequent**	*Not known*
	Stroke possibly secondary to excessive hypotension in high-risk patients (see **section 4.4**)	*Less frequent*	-
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see **sections 4.3** and **4.4**)	-	*Not known*
Eye disorders	Visual impairment	*Frequent*	*Not known*
	Myopia (see **section 4.4**)	-	*Not known*
	Acute angle-closure glaucoma	-	*Not known*
	Choroidal effusion	-	*Not known*
	Blurred vision	-	*Not known*
Ear and labyrinth disorders	Vertigo	*Frequent*	*Less frequent*
	Tinnitus	*Frequent*	-
Cardiac disorders	Palpitations	*Less frequent**	-
	Tachycardia	*Less frequent**	-

	Angina pectoris (see **section 4.4**)	*Less frequent*	-
	Dysrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation)	*Less frequent*	*Less frequent*
	Myocardial infarction possibly secondary to excessive hypotension in high risk patients (see **section 4.4**)	*Less frequent*	-
	Torsade de pointes (potentially fatal) (see **sections 4.4** and **4.5**)	-	*Not known*
Vascular disorders	Hypotension (and effects related to hypotension) (see **section 4.4**)	*Frequent*	*Less frequent*
	Vasculitis	*Less frequent**	-
	Flushing	*Less frequent**	-
	Raynaud's phenomenon	*Not known*	-
Respiratory, thoracic and mediastinal disorders	Cough (see **section 4.4**)	*Frequent*	-
	Dyspnoea	*Frequent*	-
	Bronchospasm	*Less frequent*	-
	Eosinophilic pneumonia	*Less frequent*	-
	Abdominal pain	*Frequent*	-

Gastrointestinal disorders	Constipation	*Frequent*	*Less frequent*
	Diarrhoea	*Frequent*	-
	Dyspepsia	*Frequent*	-
	Nausea	*Frequent*	*Less frequent*
	Vomiting	*Frequent*	*Less frequent*
	Dry Mouth	*Less frequent*	*Less frequent*
	Pancreatitis	*Less frequent*	*Less frequent*
Hepatobiliary disorders	Hepatitis (see **section 4.4**)	*Less frequent*	*Not known*
	Abnormal hepatic function	-	*Less frequent*
Skin and subcutaneous tissue disorders	Pruritus	*Frequent*	-
	Rash	*Frequent*	-
	Rash maculo-papular	-	*Frequent*
	Urticaria (see **section 4.4**)	*Less frequent*	*Less frequent*
	Angioedema (see **section 4.4**)	*Less frequent*	*Less frequent*
	Purpura	-	*Less frequent*
	Hyperhidrosis	*Less frequent*	-
	Photosensitivity reaction	*Less frequent**	*Not known*
	Pemphigoid	*Less frequent**	-
	Psoriasis aggravation	*Less frequent**	-
	Erythema multiforme	*Less frequent*	-
	Toxic epidermal necrolysis	-	*Less frequent*
	Stevens Johnson syndrome	-	*Less frequent*
	Muscle spasms	*Frequent*	*Not known*

Musculo-skeletal and connective tissue disorders	Possible worsening of pre-existing acute disseminated lupus erythematosus	-	*Not known*
	Arthralgia	*Less frequent**	-
	Myalgia	*Less frequent**	-
	Muscular weakness	-	*Not known*
	Rhabdomyolysis	-	*Not known*
Renal and urinary disorders	Renal failure	*Less frequent*	*Less frequent*
	Acute renal failure	*Less frequent*	*Less frequent*
	Anuria/Oliguria	*Less frequent**	-
Reproductive system and breast disorders	Erectile dysfunction	*Less frequent*	*Less frequent*
General disorders and administration site conditions	Asthenia	*Frequent*	-
	Chest pain	*Less frequent**	-
	Malaise	*Less frequent**	-
	Peripheral oedema	*Less frequent**	-
	Pyrexia	*Less frequent**	-
	Fatigue	-	*Less frequent*
Investigations	Increased blood urea	*Less frequent**	-
	Increased blood creatinine	*Less frequent**	-
	Increased blood bilirubin	*Less frequent*	-
	Increased hepatic enzymes	*Less frequent*	*Not known*

	Decreased haemoglobin and haematocrit (see **section 4.4**)	*Less frequent*	-
	Increased blood glucose	-	*Not known*
	Increased blood uric acid	-	*Not known*
	Electrocardiogram QT prolonged (see **sections 4.4** and **4.5**)	-	*Not known*
Injury, poisoning and procedural complications	Fall	*Less frequent**	-

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

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. Health care provders are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose:

Symptoms:

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

Management:

The first measures to be taken consist of rapidly eliminating the medicine(s) ingested by administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an intravenous infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.

Perindoprilat, the active form of perindopril, can be dialysed (see **section 5.2**).

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 7.1.3 Other hypotensives.

Pharmacotherapeutic group: perindopril and diuretics

ATC code: C09BA04.

TREXEVA PLUS is a combination of perindopril tosilate salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two medicines when combined.

Mechanism of action:

Linked to TREXEVA PLUS:

TREXEVA PLUS produces an additive synergy of the antihypertensive effects of the two components.

Linked to perindopril:

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

This results in:

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

The antihypertensive action of perindopril also occurs in patients with low or normal renin concentrations.

Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Perindopril reduces the work of the heart:

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

Linked to Indapamide:

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

5.2 Pharmacokinetic properties:

Linked to Perindopril/Indapamide:

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

Linked to 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 of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

Elimination:

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

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

Linearity/non-linearity:

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

Special populations:

Elderly:

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

Renal impairment:

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

In case of dialysis:

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

Cirrhosis:

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**).

Linked to indapamide:

Absorption:

Indapamide is rapidly and completely absorbed from the digestive tract.

The peak plasma level is reached in humans approximately one hour after oral administration of the medicine.

Distribution:

Plasma protein binding is 79 %.

Biotransformation:

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

Special populations:

The pharmacokinetics are unchanged in patients with renal insufficiency.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

Lactose monohydrate

Magnesium stearate

Maize, starch

Povidone K30

Sodium hydrogen carbonate

Starch, pregelatinised (maize)

Tablet coating:

Macrogol/PEG 3350

Polyvinyl alcohol-part hydrolised

Talc

Titanium dioxide E171

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

28 months.

Once the container is opened, use within 100 days.

6.4 Special precautions for storage:

Store at or below 25 °C.

Store tablets in the original package until required for use.

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container:

TREXEVA PLUS is is packaged in white opaque polypropylene tablet container with white opaque polyethylene stopper with desiccant insert equipped with a tamper-evident (TE) polyethylene flow reducer.

The tablet container is furthermore packaged in a cardboard box together with the patient information leaflet.

Pack sizes: 30, 60, 90, 90 (3x30) or 100 film-coated 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

2090

Tel.: +27 11 055 0200

8. REGISTRATION NUMBER:

TREXEVA PLUS 2,5/0,625: 48/7.1.3/1168

TREXEVA PLUS 5/1,25: 48/7.1.3/1169

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

18 December 2020

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20 October 2026