| Applicant: Teva Pharmaceuticals (Pty) Ltd. | **Product name: TREXEVA PLUS 2,5 / 0,625**<br>**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 |

**PATIENT INFORMATION LEAFLET**

**SCHEDULING STATUS:** S3

**TREXEVA PLUS 2,5/0,625 and 5/1,25 film-coated tablets**

**Perindopril tosilate/ Indapamide**

**Contains sugar**

**(TREXEVA PLUS 2,5/0,625 contains 74,056 mg lactose monohydrate and**

**TREXEVA PLUS 5/1,25 contains 148,112 mg lactose monohydrate)**

**Read all of this leaflet carefully before you start taking TREXEVA PLUS:**

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- TREXEVA PLUS has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

**What is in this leaflet:**

1. What TREXEVA PLUS is and what it is used for

2. What you need to know before you take TREXEVA PLUS

3. How to take TREXEVA PLUS

4. Possible side effects

5. How to store TREXEVA PLUS

6. Contents of the pack and other information

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**1. What TREXEVA PLUS is and what it is used for:**

TREXEVA PLUS is an anti-hypertensive medicine containing two active ingredients, perindopril and indapamide. It is an anti-hypertensive and is used in the treatment of high blood pressure (hypertension) in adults.

Perindopril belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them. Indapamide is a diuretic. Diuretics increase the amount of urine produced by the kidneys. However, indapamide is different from other diuretics, as it only causes a slight increase in the amount of urine produced. Each of the active ingredients reduces blood pressure and they work together to control your blood pressure.

It is used in the treatment of high blood pressure (hypertension) in adults.

**2. What you need to know before you take TREXEVA PLUS:**

**Do not take TREXEVA PLUS**:

- if you are hypersensitive to perindopril or any other ACE inhibitor, or to indapamide or any other sulphonamides or any of the other ingredients (listed in **section 6**)
- if you have experienced symptoms such as wheezing, swelling of the face or tongue, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema)
- if you have recurrent episodes of swelling (angioedema)
- if you have hypertrophic cardiomyopathy (cardiac muscle disease)
- if you have renal artery stenosis (narrowing of the artery supplying the kidney with blood) or if you have only one kidney functioning
- if you are pregnant or breastfeeding your baby
- if you have a severe kidney disease or if you are receiving dialysis

- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren
- if you have taken or are currently taking sacubitril/valsartan, a medicine for heart failure, as the risk of angioedema (rapid swelling under the skin in an area such as the throat) is increased (see **Warnings and precautions** and **Other medicines and TREXEVA PLUS**).
- if a method of achieving poison removal, either by dialysis or by a non-dialytic technique, such as hemoperfusion is used
- if you have severe liver impairment
- if you have low or high blood potassium
- if you have aortic stenosis (narrowing of the main blood vessel leading from the heart or if your heart's aortic valve narrows)
- if you have severe liver disease or suffer from a condition called hepatic encephalopathy (degenerative disease of the brain)
- if you take lithium or potassium-sparing diuretics (spironolactone, triamterene) as their use with TREXEVA PLUS should be avoided (see **Other medicines and TREXEVA PLUS**).
- if you have porphyria
- if you are taking anti-dysrhythmic medicines for your heart that can cause torsades de pointes
- if you are suspected of having untreated decompensated heart failure (severe water retention, difficulty in breathing)
- if you are taking fluoroquinolones (antibiotics).

**Warnings and precautions:**

Before treatment with TREXEVA PLUS, tell your doctor:

- if you think that you are (or might become) pregnant. Your doctor will normally advise you to stop taking TREXEVA PLUS before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of TREXEVA PLUS.
- if you have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood)
- if you are taking any of the following medicines used to treat high blood pressure:

- an angiotensin II receptor blocker (ARBs) (also known as sartans - for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems
- aliskiren

- if you take lithium or potassium-sparing medicines (spironolactone, triamterene) or potassium supplements as their use with TREXEVA PLUS should be avoided (see **Other medicines and TREXEVA PLUS**)
- if you suffer from a collagen disease (skin disease) such as systemic lupus erythematosus or scleroderma
- if you have a severe allergic reaction with swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema). This may occur at any time during treatment. If you develop such symptoms, you should stop taking the treatment and see a doctor immediately (see **section 4**).
- if you are of black origin since you may have a higher risk of angioedema and this medicine may be less effective in lowering your blood pressure than in non-black patients
- if you are taking any of the following medicines, the risk of angioedema is increased:

- racecadotril (used to treat diarrhoea)
- sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors (used to avoid rejection of transplanted organs)
- sacubitril (available as fixed-dose combination with valsartan), used to treat long-term heart failure.
- linagliptin, saxagliptin, sitagliptin, vildagliptin and other drugs belonging to the class of the also called gliptins (used to treat diabetes).

- if you are a haemodialysis patient dialysed with high-flux membranes
- if you have abnormally increased levels of a hormone called aldosterone in your blood (primary aldosteronism)
- if you have liver problems the use of TREXEVA PLUS may cause loss of brain function and TREXEVA PLUS should be stopped immediately
- if you have had photosensitivity reactions
- if you have kidney problems, or if you are receiving dialysis
- if you start coughing - your doctor will prescribe a different class of anti-hypertensive medicine
- if you are on a salt restricted diet or use salt substitutes which contain potassium
- if you are elderly
- if you have atherosclerosis (hardening of the arteries)
- if you have heart failure or any other heart problems
- if you have diabetes
- if you have liver problems
- if you have muscle disorders including muscle pain, tenderness, weakness or cramps
- if you suffer from hyperparathyroidism (overactive parathyroid gland)
- if you suffer from gout
- if you experience a decrease in vision or eye pain. These could be symptoms of fluid accumulation in the vascular layer of the eye (choroidal effusion) or an increase of pressure in your eye and can happen within hours to weeks of taking TREXEVA PLUS. This can lead to permanent vision loss, if not treated. If you earlier have had a penicillin or sulfonamide allergy, you can be at higher risk of developing this.

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

When you are taking TREXEVA PLUS, you should also inform your doctor or the medical staff:

- if you are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- if you are to undergo dialysis or LDL apheresis (which is removal of cholesterol from your blood by a machine)
- if you have recently suffered from diarrhoea or vomiting, or are dehydrated
- if you are to undergo anaesthesia and/or surgery
- if you have changes in your vision or pain in one or both of your eyes while taking TREXEVA PLUS. This could be a sign that you are developing glaucoma, increased pressure in your eye(s). You should discontinue TREXEVA PLUS treatment and seek medical attention
- if you are to undergo a medical test that requires injection of an iodinated contrast medicine (a substance that makes organs like kidney or stomach visible on an X-ray)

Athletes should be aware that TREXEVA PLUS contains an active ingredient (indapamide) which may give a positive reaction in drug tests.

**Children and adolescents:**

TREXEVA PLUS is not for use in children and adolescents under 18 years.

**Other medicines and TREXEVA PLUS:**

Always tell your healthcare provider if you are taking any other medicine.

(This includes all complementary or traditional medicines.)

You should not take TREXEVA PLUS with:

- lithium (used to treat mania or depression)
- aliskiren (medicine used to treat hypertension) if you have no diabetes mellitus or kidney problems

- other medicines used to treat high blood pressure: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, including angiotensin II receptor blocker (ARB) or diuretics (medicines which increase the amount of urine produced by the kidneys)
- potassium-sparing diuretics (e.g. triamterene, amiloride), potassium salts, other medicines which can increase potassium in your body (such as heparin and co-trimoxazole also known as trimethoprim/sultamethoxazole for infections caused by bacteria)
- sacubitril/valsartan (used to treat long-term heart failure)
- estramustine (used in cancer therapy)
- medicines, which are most often used to treat diarrhoea (racecadotril or avoid rejection of transplanted organs (sirolimus, everolimus, temsirolimus and other medicines belonging to the class of so-called mTor inhibitors). See section **Warnings and precautions.**
- fluoroquinolones (as antibiotic).

Make sure to tell your doctor if you are taking any of the following medicines as special care may be required:

- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis)
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) or high dose salicylates (e.g. aspirin) (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting)
- medicines to treat mental disorders such as depression, anxiety, schizophrenia (e.g. tricyclic antidepressants, neuroleptics (such as amisulpride, sulpiride, sultopride, tiapride, haloperidol, droperidol))
- medicines to treat diabetes such as insulin, metformin or gliptins
- potassium-sparing medicines used in the treatment of heart failure: eplerenone and spironolactone at doses between 12.5 mg to 50 mg per day
- allopurinol (for the treatment of gout)
- corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis

- immunosuppressants used for the treatment of auto-immune disorders or following transplant surgery to prevent rejection (e.g. ciclosporin)
- procainamide (for the treatment of an irregular heartbeat)
- anaesthetic medicines
- injectable gold (used to treat rheumatoid polyarthritis)
- medicines used for heart rhythm problems (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol)
- vasodilators including nitrates medicines that make the blood vessels become wider)
- digoxin or other cardiac glycosides (for the treatment of heart problems),
- sultopride (for the treatment of psychoses)
- cisapride, diphemanil (used to treat gastric and digestive problems)
- bepridil (used to treat angina pectoris)
- erythromycin by injection (an antibiotic)
- moxifloxacin, sparfloxacin (antibiotic: medicine used to treat infection)
- methadone (used to treat addiction)
- vincamine (used to treat symptomatic cognitive disorders in elderly including memory loss)
- halofantrine (used to treat certain types of malaria)
- terfenadine, mizolastine or astemizole (antihistamines for hay fever or allergies)
- pentamidine (used to treat pneumonia)
- amphotericin B by injection (to treat severe fungal disease)
- stimulant laxatives (e.g. senna)
- tetracosactide (to treat Crohn's disease)
- iodinated contrast medicine
- calcium including calcium supplements.
- trimethoprim (for the treatment of infections)

**TREXEVA PLUS with food and drink:**

It is preferable to take TREXEVA PLUS in the morning before a meal.

**Pregnancy, breastfeeding and fertility:**

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby please consult your doctor, pharmacist or other healthcare provider for advice before taking TREXEVA PLUS.

You should not take TREXEVA PLUS if you are pregnant or breastfeeding your baby.

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

**Driving and using machines:**

TREXEVA PLUS does not affect alertness but different reactions such as dizziness or weakness in relation to the decrease in blood pressure may occur in certain patients. If affected, your ability to drive or to operate machinery may be impaired.

It is not always possible to predict to what extent TREXEVA PLUS may interfere with your daily activities. You should ensure that you do not engage in driving a vehicle or use of machines until you are aware of the measure to which TREXEVA PLUS affects you.

**TREXEVA PLUS contains lactose monohydrate and sodium hydrogen carbonate:**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking TREXEVA PLUS.

TREXEVA PLUS contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

**3. How to take TREXEVA PLUS:**

Do not share medicines prescribed for you with any other person.

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

The recommended dose is one tablet once a day. Your doctor may decide to modify the dosage regimen if you suffer from renal impairment. Take your tablet preferably in the morning and before a meal. Swallow the tablet with a glass of water.

Your doctor will tell you how long your treatment with TREXEVA PLUS will last. If you have the impression that the effect of TREXEVA PLUS is too strong or too weak, tell your doctor or pharmacist.

**If you take more TREXEVA PLUS than you should:**

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

The most likely effect in case of overdose is low blood pressure (associated with nausea, vomiting, cramps, dizziness or fainting, sleepiness, mental confusion, changes in the amount of urine produced by kidneys). If this happens, lying down with the legs raised can help.

**If you forget to take TREXEVA PLUS:**

Take the next dose at the usual time. Do not take a double dose to make up for forgotten individual doses.

**If you stop taking TREXEVA PLUS:**

As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping TREXEVA PLUS.

**4. Possible side effects:**

TREXEVA PLUS can have side effects

Not all side effects reported for TREXEVA PLUS are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking TREXEVA PLUS, please consult your healthcare provider for advice.

If any of the following happens, stop taking TREXEVA PLUS and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing (see **section 2, Warnings and precautions**),
- rash or itching,
- fainting.

These are all very serious side effects. If you have them, you may have had a serious reaction to TREXEVA PLUS. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- weakness of arms or legs, or problems speaking which could be a sign of a possible stroke
- cardiovascular disorders - palpitations (awareness of your heartbeat), tachycardia (fast heartbeat), dysrhythmia (irregular heartbeat), angina pectoris (pains to the chest, jaw and back, brought on by physical effort) and myocardial infarction (heart attack)
- severe dizziness or fainting due to low blood pressure
- bronchospasm (tightening of the chest, wheezing and shortness of breath
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell

- yellowing of the skin or eyes (jaundice) which could be a sign of hepatitis
- severe skin reactions including erythema multiforme (a skin rash which often starts with red itchy patches on your face, arms or legs) or intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome) or other allergic reactions
- degenerative disease in the brain caused by liver illness (Hepatic encephalopathy) - you may experience extreme anxiety, difficulty thinking, severe confusion, concentrating accompanied by a musty sweet breath odour, slurred speech and unusual movement of hands/arms (shaking hands)
- life-threatening irregular beat (Torsade de pointes)
- muscle weakness, cramps, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

*Frequent side effects:*

- hypokalaemia (low potassium in the blood)
- headache
- feelings of dizziness
- pins and needles
- taste disturbances
- visual impairment
- vertigo (spinning of head)
- tinnitus (sensation of noises in the ears)
- cough

- shortness of breath (dyspnoea)
- abdominal pain
- constipation
- diarrhoea
- indigestion
- nausea, vomiting
- allergic reactions (skin rashes, itching)
- muscle cramps
- feeling of tiredness

*Less frequent side effects:*

- runny nose
- dark urine, feeling sick (nausea) or being sick (vomiting), muscle cramps, confusion and seizures. These may be symptoms of a condition called SIADH (inappropriate antidiuretic hormone secretion)
- unusual bruising or easy bleeding, feeling generally tired or lethargic, pale skin, signs of infection such as sore throat, fever and chills (these may indicate changes or damage to your blood cells including a lower number of white and red blood cells, lower number of blood platelets and an excess of eosinophils (a type of white blood cell)
- hypoglycaemia (very low blood sugar level)
- changes in blood composition (levels of potassium, sodium, chloride, magnesium and calcium) that have the following symptoms: tiredness or weakness, nausea and vomiting, irregular heartbeats, confusion, seizures, loss of appetite, abdominal pain, disorientation
- depression
- mood swings, sleep disturbances
- confusion

- sleeplessness
- inflammation of blood vessels that results in a reddish rash, fever, loss of appetite and fatigue
- flushing
- eosinophilic pneumonia (a rare type of pneumonia)
- dry mouth
- abnormal hepatic function (skin and eyes appear yellowish, abdominal pain, dark urine colour)
- hives
- red pinpoints on skin
- excessive sweating
- photosensitivity reactions (increased sensitivity of the skin to sun)
- rare autoimmune conditions that cause blistering and rashes on the skin and mucous membranes
- flare-ups of psoriasis
- joint pain
- muscle pain
- kidney problems
- acute renal failure
- decreased or absent urine output
- impotence (inability to obtain or maintain an erection)
- chest pain, fever, general feeling of discomfort
- swelling of the lower legs and arms (peripheral oedema)
- tiredness or fatigue
- changes in blood values and laboratory parameters: increased blood urea, increased blood creatinine, increased level of liver enzymes, high level of serum bilirubin and lower haemoglobin
- fall

*Frequency not known:*

- short sightedness (myopia), blurred vision
- decrease in vision or pain in your eyes due to high pressure (possible signs of fluid accumulation in the vascular layer on the eye (choroidal effusion) or acute angle-closure glaucoma)
- numbness and pain in fingers or toes (Raynaud's phenomenon)
- worsening of a disease called systemic lupus erythematosus (a type of collagen disease that causes severe fatigue, joint pain and swelling, rash on the cheeks and nose called a "butterfly rash").
- incorrect results for heart tests (ECG)
- high uric acid levels in the blood that cause fever, chills, fatigue, joint inflammation (called "gout")
- high sugar levels in the blood that causes increased thirst, frequent urination, fatigue

Disorders of the blood, kidney, liver or pancreas and changes in laboratory parameters (blood tests) can occur. Your doctor may need to give you blood tests to monitor your condition.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

**Reporting of side effects:**

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. By reporting side effects, you can help provide more information on the safety of TREXEVA PLUS.

**5. How to store TREXEVA PLUS:**

Store all medicine out of reach of children.

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.

Once the container is opened, use within 100 days.

Do not use the tablets after the expiry date shown on the container.

Return the expired medicine to your pharmacist for safe disposal.

**6. Contents of the pack and other information:**

**What TREXEVA PLUS contains:**

The active ingredients are perindopril tosilate and indapamide.

The other ingredients are lactose monohydrate, magnesium stearate, maize; starch, povidone K30, sodium hydrogen carbonate, starch pregelatinized, macrogol/PEG 3350, polyvinyl alcohol-part hydrolised, talc and titanium dioxide E171.

**What TREXEVA PLUS looks like and contents of the pack:**

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 mg/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.

TREXEVA PLUS 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.

**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


**This leaflet was last revised in:**

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**REGISTRATION NUMBER:**

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

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