Package leaflet: Information for patient

ZADA PHARMACEUTICALS

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Keep this leaflet. You may need to read it again. If you have any further questions, ask your doctor or pharmacist. This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

KADRIL PLUS 10 mg/25 mg Tablets
KADRIL PLUS 20 mg/12.5 mg Tablets
Enalapril maleate/hydrochlorothiazide

What is in this leaflet

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

KADRIL PLUS contains a combination of enalapril maleate and hydrochlorothiazide:
- Enalapril belongs to a group of medicines called angiotensin converting enzyme inhibitors (ACE inhibitors), which lower blood pressure by widening your blood vessels.
- Hydrochlorothiazide belongs to a group of drugs called diuretics ('water tablets'), which lower blood pressure by increasing the volume of urine you produce.

KADRIL PLUS is used when treatment with enalapril as a single agent on its own has proven insufficient.
Your doctor may also prescribe **KADRIL PLUS** instead of separate tablets of the same doses of enalapril and hydrochlorothiazide. This fixed dose combination is not suitable for initial therapy.

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

Do not take KADRIL PLUS:
- if you are allergic to enalapril, hydrochlorothiazide or any of the other ingredients of this medicine (listed in section 6)
- if you have severe kidney problems
- if you are not passing urine
- if you have previously suffered from swelling of the extremities, face, lips, throat, mouth or tongue (angioedema) when treated with other ACE inhibitors such as ramipril or under any other circumstances
- if someone in your family has previously suffered from swelling of the extremities, face, lips, throat, mouth or tongue (angioedema)
- if you are allergic to a type of medicine called 'sulphonamides'
- if you are more than 3 months pregnant. (It is also better to avoid Enalapril Maleate and Hydrochlorothiazide in early pregnancy - see pregnancy section)
- if you have severe liver problems
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

Do not take **KADRIL PLUS** if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking **KADRIL PLUS**.

Warnings and precautions
Talk to your doctor or pharmacist before taking **KADRIL PLUS**:
- if you have kidney problems, such as 'renal artery stenosis' (reduced blood flow to the kidney),
- have had a recent kidney transplantation, are a dialysis patient, or are taking 'water tablets' (diuretics)
- if you have blood disorders or liver problems
- if you have low blood pressure, are on a salt restricted diet, or have suffered from excessive vomiting or diarrhoea recently
- if you have a heart condition called 'ischaemic heart disease' which reduces the blood supply to the heart muscles
- if you have a heart condition called 'aortic stenosis', 'hypertrophic cardiomyopathy' or 'outflow obstruction'
- if you have a condition affecting the blood supply to your brain (cerebrovascular disease)
- if you have heart failure
- if you have collagen vascular disease such as systemic lupus erythematosus (SLE) or scleroderma, which may be associated with skin rashes, joint pain and fever
- if you are taking immunosuppressant therapy (used for the treatment of autoimmune disorders such as rheumatoid arthritis or following transplant surgery)
- if you are taking any of the following medicines, the risk of angioedema (rapid swelling under the skin in areas such as the throat) is increased:
- sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors (used to avoid rejection of transplanted organs)
- if you suffer from gout or are taking allopurinol (used for the treatment of gout), or procainamide (used to treat abnormal heart rhythms)
- if you have a history of 'angioedema' while taking other medicines. The signs may have been itching, nettle rash, wheezing or swelling of your hands, throat, mouth or eyelids (see section 4)
- if you have diabetes and are taking antidiabetic medicines, including insulin to control your diabetes (you should monitor your blood for low blood glucose levels, especially during the first month of treatment)
- if you are taking potassium supplements or potassium containing salt substitutes
- if you are taking other medicines that can affect the level of potassium in your blood, such as heparin (an anticoagulant)
- if you have high levels of potassium in the blood
- if you are taking lithium, used for the treatment of some psychiatric illnesses
- if you have abnormal levels of water and minerals in your body (fluid/electrolyte imbalance)
- if you are going to have tests to check your parathyroid function
- if you have allergy problems or asthma
- 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 have had skin cancer or if you develop an unexpected skin lesion during the treatment.

Treatment with hydrochlorothiazide, particularly long term use with high doses, may increase the risk of some types of skin and lip cancer (non-melanoma skin cancer). Protect your skin from sun exposure and UV rays while taking **KADRIL PLUS**.
Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.
See also information under the heading “Do not take **KADRIL PLUS**”.
You must tell your doctor if you think you are (or might become) pregnant.
KADRIL PLUS is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
You should be aware that this medicine may be less effective at lowering the blood pressure in black patients than in non-black patients.
If you are about to have any of the following procedures, you should tell your doctor who is treating you that you are taking **KADRIL PLUS**:
- any surgery or receive anaesthetics (even at the dentist)
- a treatment called LDL apheresis, to remove cholesterol from your blood using a machine
- desensitisation treatment, to reduce the effect of an allergy to bee or wasp stings.

Routine tests
When you first start to take **KADRIL PLUS**, your doctor will monitor your blood pressure frequently to ensure you have been given the correct dose. In addition, for some patients the doctor may want to do some tests to measure your potassium, sodium, magnesium, creatinine and liver enzyme levels.
Tell your doctor if you have taken or will need to take an anti-doping test, as this medicine can produce a positive result.

Children
KADRIL PLUS is not recommended for use in children.

Other medicines and KADRIL PLUS
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription as some drugs may affect each other's action. Also some other medicines can affect the way **KADRIL PLUS** works. This applies in particular if you are also taking:
- medicines which are most often used to avoid rejection of transplanted organs (sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors). See section “Warnings and precautions”.
- potassium sparing 'water tablets' (diuretics) such as spironolactone, eplerenone, triamterene or amiloride, potassium supplements, or potassium-containing salt substitutes. Enalapril Maleate and Hydrochlorothiazide may increase the levels of potassium in your blood leading to high potassium levels. This causes few signs and is usually seen by a test 'water tablets' (diuretics such as thiazides, furosemide, bumetanide), in particular those so called potassium sparing, other drugs which can increase potassium in your body (such as heparin and co-trimoxazole also known as trimethoprim/sulfamethoxazole)
- other medicines that lower blood pressure, such as nitroglycerine, nitrates, vasodilators, methyldopa and angiotensin II receptor antagonists (e.g. candesartan, irbesartan and losartan)lithium, used for the treatment of some psychiatric illnesses. Enalapril Maleate and Hydrochlorothiazide should not be taken with this drug
- barbiturates (sedatives used for sleeplessness or epilepsy)
- tricyclic antidepressants such as amitriptyline, used for depression and antipsychotics such as phenothiazines, used for severe anxiety
- painkillers such as morphine or anaesthetics, because your blood pressure may become too low
- cholestyramine or colestipol (used to help control cholesterol levels)
- medicines used for, stiffness and inflammation associated with painful conditions, particularly those affecting your muscles, bones and joints including:
- gold therapy (sodium aurothiomalate) which can lead to flushing of your face, feeling sick (nausea), vomiting and low blood pressure, when taken with Enalapril Maleate and Hydrochlorothiazide, and
- non-steroidal anti-inflammatory drugs (NSAIDs), for example diflunisal or diclofenac.

They may prevent your blood pressure from being well controlled and may increase the level of potassium in your blood
- medicines such as ephedrine, used in some cough and cold remedies, or noradrenaline and adrenaline used for low blood pressure, shock, cardiac failure, asthma or allergies. If used with **KADRIL PLUS** these drugs may keep your blood pressure high
- corticotropin (ACTH), used to test whether your adrenal glands are working properly
- corticosteroids (used to treat certain conditions such as rheumatism, arthritis, allergic conditions, asthma or certain blood disorders)
- probenecid, sulfinpyrazone and allopurinol (used to treat gout)
- ciclosporin (immunosuppressive agents used for autoimmune disorders)
- medicines for the treatment of cancer such as cyclophosphamide or methotrexate
- antacids (used for indigestion relief)
- procainamide, amiodarone, sotalol, quinidine, hydroquinidine, disopyramide, dofetilide or ibutilide (used to treat abnormal heart rhythms)
- digitalis (used to treat heart rhythm problems)
- carbenoxolone (used to treat stomach ulcers)
- excessive use of laxatives
- antidiabetic medicines such as insulin and metformin. Enalapril Maleate and Hydrochlorothiazide may cause your blood sugar levels to drop even further if you take it with antidiabetics
- anti-pain and anti-inflammatory drugs, such as acetylsalicylic acid (more than 300 mg/day)
- muscle relaxants, e.g. tubocurarine chloride used to relax the muscles during operations
- salts of calcium and vitamin D
- carbamazepine used to treat epilepsy or bipolar disorder
- amphoteracin B used to treat fungal infections
- iodinated contrast agents used in X-ray procedures
- medicines such as atropine or biperiden.

Your doctor may need to change your dose and/or to take other precautions:
- if you are taking an angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings “Do not take **KADRIL PLUS”** and “Warnings and precautions”).

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking **KADRIL PLUS**.

KADRIL PLUS with alcohol
If you drink alcohol while taking **KADRIL PLUS**, it may cause your blood pressure to drop too much and you may experience dizziness, light-headedness or faintness. You should keep your alcohol intake to a minimum.

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

Breast-feeding
Tell your doctor if you are breast-feeding or about to start breast-feeding.
KADRIL PLUS is not recommended for mothers who are breast-feeding.
Driving and using machines
Certain side effects, such as dizziness and weariness, have been reported with **KADRIL PLUS**, which may affect some patients' ability to drive or operate machinery. If you experience any of these effects, do not drive and use machines.
KADRIL PLUS contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take KADRIL PLUS
Always take this medicine 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 taken once a day.
Elderly
Your doctor will adjust the dose of **KADRIL PLUS** carefully.
Kidney problems
Your doctor will adjust the dose of **KADRIL PLUS** carefully.
Use in children
KADRIL PLUS is not recommended for use in children.
Method of administration
KADRIL PLUS can be used with or without food.
The tablets should be swallowed with a drink of water.
The tablets can be divided into equal doses.
If you take more KADRIL PLUS than you should
If you (or someone else) swallow a lot of the tablets at the same time, or if you think a child hasswallowed any of the tablets, seek medical advice immediately. An overdose is likely to cause low blood pressure, an excessively fast or slow heart beat, palpitations (a feeling of unduly rapid or irregular heart beat), shock, rapid breathing, cough, feeling and being sick, cramps, dizziness, feeling sleepy and confused or anxious, excessive urination or not being able to urinate.
Take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.
If you forget to take KADRIL PLUS
Do not take a double dose to make up for a forgotten tablet, take your next dose at the normal time.
If you have any further questions on the use of this product, ask your doctor or pharmacist.
If you stop taking KADRIL PLUS
The treatment of hypertension is a long term treatment and you should consult your doctor before stopping treatment. Interruption or discontinuation of your treatment could cause your blood pressure to increase.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
If you think you may have any of the following side effects, stop taking **KADRIL PLUS** and contact your doctor or go to your nearest hospital emergency room immediately:
Common: may affect up to 1 in 10 people:
- a severe allergic reaction with symptoms such as rash, itching, shortness of breath or wheezing, swelling of your hands, face, eyes, lips, tongue, mouth or throat, which may cause difficulty in swallowing (called angioedema). You should be aware that black patients are at an increased risk of these types of reactions to ACE inhibitors.
- pain with a feeling of tightness, pressure or heaviness in the chest (angina)
- severe dizziness, light-headedness, especially at the start of treatment or when you stand up.

Uncommon: may affect up to 1 in 100 people:
- inflammation of the pancreas, which causes severe pain in the abdomen and back (pancreatitis)
- heart attack or stroke (in high risk patients)
- persistent constipation with discomfort or bloating, possibly with feeling or being sick. These may be signs of a blockage in the gut
- burning, aching pain in the stomach with an empty feeling and hunger, particularly when the stomach is empty. These may be signs of an ulcer
- difficulty or pain when urinating, with blood in the urine or changes in the colour or amount of urine passed. Pain in the lower back, feeling or being sick, feeling generally unwell. These may be signs of serious problems with your kidneys
- changes to the number of certain cells in your blood that may cause you to feel more tired than usual, weak, short of breath or have pale skin (fewer red blood cells), have more frequent infections with fever, chills, sore throat of mouth ulcers (fewer white blood cells), or to bleed or bruise more easily or for longer than usual (fewer platelets).

Rare: may affect up to 1 in 1,000 people:
- skin rash, which may blister and looks like small targets – central dark spots surrounded by a paler area, with a dark ring around the edge (erythema multiforme)
- blistering of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome)
- skin looks as if it were burnt and peeling off (toxic epidermal necrolysis)
- a condition causing blisters and lesions normally starting in the mouth (pemphigus), nettlerash,
- hair loss and itching. Sometimes skin problems may be accompanied by fever, serious inflammation,
- inflammation of the blood vessels, muscle pain and/or joint pain, changes in blood composition and an increase in sedimentation rate (a blood test to detect inflammation)
- severe breathing difficulties, including when resting, generally feeling unwell with increased shivering, fever, sweating, cough or wheezing
- feeling sick (nausea) or being sick (vomiting), loss of appetite, feeling generally unwell, fever, itching,
- yellowing of the skin and whites of the eyes (jaundice), light coloured bowel motions and dark coloured urine which may be signs of severe liver problems or hepatitis.

Not known: frequency cannot be estimated from the available data:
- swollen and sore saliva glands
- a lower than normal level of sodium in the blood, which may make you feel weak and confused with aching of muscles. This may be due to inappropriate ADH secretion, a hormone that causes the body to retain water and dilute the blood, reducing the amount of sodium.
- skin and lip cancer (Non-melanoma skin cancer).

Other possible side effects
A dry cough, which may persist for a long time, has been reported very commonly (may affect more than 1 in 10 people) with the use of enalapril/hydrochlorothiazide and other ACE inhibitors, but may be also a symptom of other upper respiratory tract disease. You should contact your doctor if you develop this symptom.
Very common: may affect more than 1 in 10 people:
- blurred vision
- dizziness
- feeling sick (nausea)
- weakness.

Common: may affect up to 1 in 10 people:
- headache, depression, fainting
- low blood pressure (which may make you feel dizzy when you stand up)
- chest pain
- heart rhythm changes, fast heart beat
- shortness of breath
- diarrhoea, pain around your stomach area (abdomen), changes in taste, feeling tired
- rash
- increased blood potassium level, increases in serum creatinine (both are usually detected by a test)
- low levels of potassium in the blood, which can cause muscle weakness, twitching or abnormal heart rhythm, increased levels of cholesterol, increased levels of triglycerides, increased levels of uric acid in the blood
- muscle cramps.

Uncommon: may affect up to 1 in100 people:
- a sense of heightened awareness or a shaky feeling (caused by low blood sugar)
- confusion, feeling sleepy, difficulty sleeping, feeling nervous, tingling or numbness, feeling like you are spinning (vertigo)
- flushing, racing or uneven heart beats
- runny nose, sore throat and hoarseness, difficulty breathing or wheezing
- being sick, indigestion, constipation, loss of appetite, stomach irritation, dry mouth, flatulence
- excessive sweating, itching, hives (urticaria), hair loss
- kidney problems, protein in your urine (usually detected by a test)
- impotence, decreased libido
- high temperature, weakness (malaise)
- ringing in your ears
- increases in blood urea and decreases in blood sodium levels (usually detected by a test)
- low level of magnesium in the blood (hypomagnesemia)
- joint pain, disease with painful swollen joints caused by uric acid crystals (gout).

Rare: may affect up to 1 in 1,000 people:
- strange dreams, sleeping problems, weakness causing loss of movement
- swollen lymph glands in the throat, armpits or groin
- low blood flow to your fingers and toes causing redness and pain (Raynaud's)
- runny or sore nose
- pain, swelling or ulcers in your mouth, infection or pain and swelling of your tongue
- passing less urine than usual
- swollen nasal lining
- difficulty breathing, respiratory distress
- flaking or peeling of the skin, excessive redness of your skin, blisters, purple or red-brown spots visible through the skin
- development of breasts in men
- increased liver enzymes or liver waste products (usually detected by a blood test)
- increases in blood sugar or decreases in the amount of haemoglobin in the blood (usually detected by a blood test)
- inflammation of the gallbladder.

Very rare: may affect up to 1 in 10,000 people:
- swelling in the intestines. Signs may include stomach pain, feeling sick and vomiting
- elevated calcium level in blood causing abdominal pain, feeling and being sick, constipation, loss of appetite, excessive thirst, excessive urination, tiredness, weakness and weight loss.

Not known: frequency cannot be estimated from the available data:
- sugar (glucose) in the urine
- light-headedness.

In some patients, a group of side effects may be seen at the same time. These can include fever, problems caused by inflammation or changes to blood cells (some of which may require urgent medical attention – see the start of this section), painful or swollen joints and skin problems, which may include unusual sensitivity to sunlight.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store KADRIL PLUS
Do not store above 25°C. Store in the original package. Keep out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

6. Contents of the pack and other information
What KADRIL PLUS contains
The active ingredients are **KADRIL PLUS**. Each tablet contains 20 mg of enalapril maleate and 12.5 mg of hydrochlorothiazide.
The other ingredients are: lactose monohydrate, sodium bicarbonate, povidone, pregelatinized corn starch, corn starch, maleic acid, magnesium stearate.

What KADRIL PLUS looks like and contents of the pack
KADRIL PLUS 10 mg/25 mg tablets: Box of 20 round, biconvex tablets,yellow, of 10 mg enalapril maleate + 25mg hydrochlorothiazide in blister pack (2 blisters x 10 tablets).
KADRIL PLUS 20 mg/12.5 mg tablets Box of 20 round, biconvex tablets, white, of 20 mg enalapril maleate + 12,5 mg hydrochlorothiazide in blister pack (2 blisters x 10 tablets)

Marketing Authorisation Holder
ZADA Pharmaceuticals Ltd.
Donji Bistarac without number
75300 Lukavac
Bosnia and Herzegovina

Date and number of renewal of marketing authorization
KADRIL PLUS, 20 tablets x (10 + 25) mg in box:
Number: 04-07.3-2-4861/15 **Date:** 09.09.2015.
KADRIL PLUS, 20 tablets x (20 + 12,5) mg in box:
Number: 04-07.3-2-4862/15 **Date:** 09.09.2015.
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