APPROVED PIL

For

MIXANVAL

Registration No.:

Mixanval 5 mg/5 mg tablets: 43/7.1.3/0937
Mixanval 5 mg/10 mg tablets: 43/7.1.3/0938
Mixanval 10 mg/5 mg tablets: 43/7.1.3/0939
Mixanval 10 mg/10 mg tablets: 43/7.1.3/0940

Date Approved: April 2020

Confidential Information

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S3

Mixanval 5 mg / 5 mg tabletss

Mixanval 5 mg / 10 mg tablets

Mixanval 10 mg / 5 mg tablets

Mixanval 10 mg / 10 mg tablets

perindopril arginine/amlodipine

Contains sugar (lactose)

Read this entire leaflet carefully before you start taking Mixanval.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist, nurse or other healthcare provider.
- **Mixanval** has been prescribed to 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 **Mixanval** is and what it is used for
2. What you need to know before you take **Mixanval**
3. How to take **Mixanval**
4. Possible side effects
5. How to store **Mixanval**
6. Contents of the pack and other information

1. What Mixanval is and what it is used for

Mixanval is used for the treatment of high blood pressure (hypertension). Patients already stabilised on perindopril and amlodipine in separate tablets may instead switch to one tablet of **Mixanval** which contains both ingredients.

Mixanval is a combination of two active ingredients, perindopril and amlodipine. Perindopril is an ACE-inhibitor (angiotensin converting enzyme). Amlodipine is a calcium antagonist (which belongs to a class of medicines called dihydropyridines). Together perindopril and amlodipine widen and relax the blood vessels to reduce blood pressure.

2. What you need to know before you take Mixanval

Do not take Mixanval

- If you are hypersensitive (allergic) to perindopril or any other ACE-inhibitor, or to amlodipine or any other calcium antagonists, or any of the other ingredients of **Mixanval**.
- 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 diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren,
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body),
- Hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery which supplies the kidney with blood),
- If you have severe kidney damage,
- If you have porphyria,
- If you have severe low blood pressure (hypotension),

- If you suffer from heart failure after a heart attack,
- if you are having dialysis or any other type of blood filtration. Depending on the machine that is used, **Mixanval** may not be suitable for you,
- if you have kidney problems where the blood supply to your kidneys is reduced (renal artery stenosis),
- if you are being treated with sacubitril/valsartan, a medicine for heart failure. (see "Take special care" and "Taking other medicines with **Mixanval**"),
- If you take lithium (used to treat mania or depression),
- If you take estramustine (used in cancer therapy),
- If you take potassium-sparing diuretics (spironolactone, triamterene), potassium supplements or potassium-containing salt substitutes,
- if you are taking fluoroquinolones (an antibiotic),
- If you are breastfeeding (see Pregnancy, breastfeeding and fertility),
- If you are pregnant or planning to be pregnant (see Pregnancy, breastfeeding and fertility),

Warnings and precautions

If you have any of the following, please talk to your doctor before taking **Mixanval**:

- hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery which supplies the kidney with blood)
- Heart failure
- Severe increase in blood pressure (hypertensive crisis)
- Any other heart problems
- Liver problems
- Kidney problems or if you are receiving dialysis
- Abnormally increased levels of a hormone called aldosterone in your blood (primary aldosteronism)

- Collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma
- Diabetes
- If you are on a salt restricted diet (a well-balanced potassium blood level is essential)
- if you are elderly and your dose needs to be increased
- 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
- Contact your doctor to re-evaluate your treatment if you are treated with ACE-inhibitors/Angiotansin receptor blockers together with a fluoroquinolone antibiotic.

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 Mixanval”.

If are taking any of the following medicines, the risk of angioedema is increased:

- racecadotril (used to treat diarrhoea)
- sirolimus, everolimus, temsirolimus and other medicines 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.

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.

Angioedema:

Angioedema (a severe allergic reaction with swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing) has been reported in patients treated with ACE-inhibitors, including **Mixanval**. This may occur at any time during treatment. If you develop such symptoms, you should stop taking **Mixanval** and see a doctor immediately.

When you are taking **Mixanval**, you should also inform your doctor or the medical staff if you:

- Are going to have a general anaesthetic and/or major surgery,
- Have recently suffered from diarrhoea or vomiting (being sick),
- Are to undergo LDL apheresis (the removal of cholesterol from your blood by a machine),
- Are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings.

Mixanval is not recommended for use in children and adolescents.

Other medicines with Mixanval:

Always tell your healthcare provider if you are taking any other medicine. (This includes complimentary or traditional medicines).

You should avoid taking **Mixanval** with:

- lithium (used to treat mania or depression)
- estramustine (used in cancer therapy)
- potassium-sparing diuretics (triamterene, amiloride), potassium supplements or potassium-containing salt substitutes, other drugs which can increase potassium in your body (such as heparin and co-trimoxazole also known as trimethoprim/sulfamethoxazole),
- potassium-sparing medicines used in the treatment of heart failure: eplerenone and spironolactone at doses between 12,5 mg to 50 mg by day.

Treatment with **Mixanval** can be affected by other medicines. Make sure to tell your doctor if you are taking any of the following medicines as special care may be required:

- Other medicines for high blood pressure, including angiotensin II receptor blocker (ARB), aliskiren (see Do not take **Mixanval**) or diuretics (medicines which increase the amount of urine produced by the kidneys)
- Medicines, which are most often used to treat diarrhoea (racecadotril) or avoid rejection of transplanted organs (sirolimus, everolimus, temsirolimus and other drugs belonging to the class of so-called mTor inhibitors)
- Sacubitril/valsartan (used to treat long-term heart failure). See section “Do not take **Mixanval**
- Non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or high dose aspirin
- Medicines to treat diabetes (such as insulin)
- Medicines to treat mental disorders such as depression, anxiety, schizophrenia etc. (e.g. tricyclic antidepressants, antipsychotics, imipramine-like antidepressants, neuroleptics)
- Immunosuppressants (medicines which reduce the defence mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin, tracolimus)
- Trimethoprim and co-trimoxazole (for the treatment of infections)
- Allopurinol (for the treatment of gout)
- Procainamide (for the treatment of an irregular heart beat)
- Vasodilators including nitrates (products that widen the blood vessels)
- Ephedrine, norepinephrine (noradrenaline) or ephedrine (adrenaline) (medicines used to treat low blood pressure, shock or asthma)
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- Baclofen or dantrolene (infusion) both used to treat muscle stiffness in diseases such as multiple sclerosis; dantrolene is also used to treat malignant hyperthermia during anaesthesia (symptoms including very high fever and muscle stiffness)
- Some antibiotics such as rifampicin, erythromycin, clarithromycin
- Fluoroquinolones (an antibiotic) it may cause acute kidney disease
- *Hypericum perforatum* (St John's wort, an herbal medicine used to treat depression)
- Simvastatin (cholesterol lowering medicine)
- Anti-epileptic agents such as carbamazepine, phenobarbital, phenytoin, primidone.
- Itraconazole, ketoconazole (medicines used for treatment of fungal infections).
- Alpha-blockers used for the treatment of enlarged prostate such as prazosin, alfuzosin, doxazosin, tamsulosin, terazosin
- Amifostine (used to prevent or reduce side effects caused by other medicines or radiation therapy that are used to treat cancer)
- Corticosteroids (used to treat various conditions including severe asthma and rheumatoid arthritis)
- Gold salts, especially with intravenous administration (used to treat symptoms of rheumatoid arthritis)
- Ritonavir, indinavir, nelfinavir (so called protease inhibitors to treat HIV).

Mixanval with food and drink:

Mixanval should be taken in the morning before breakfast.

Grapefruit juice and grapefruit should not be consumed by people who are taking **Mixanval**. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of **Mixanval**.

Pregnancy and breastfeeding and fertility

If you are pregnant or breastfeeding your baby while taking this medicine, please consult your doctor, pharmacist or other health care provider for advice before taking this medicine.

You must tell your doctor if you think that you are (or might become) pregnant. Your doctor will advise you to take another blood pressure lowering medicine instead of **Mixanval**, as **Mixanval** is contraindicated in pregnancy, and may cause serious harm to your baby if it is used in pregnancy. You should be switched to another blood pressure lowering medicine to replace **Mixanval** before you become pregnant.

Your doctor will normally advise you to stop taking **Mixanval** as soon as you know you are pregnant. If you become pregnant during therapy with **Mixanval**, please inform and see your doctor without delay.

The use of **Mixanval** is not recommended during breastfeeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Mixanval may cause dizziness, weakness, tired, feeling sick, or may give you a headache due to low blood pressure which could affect your ability to drive or operate machinery.

Mixanval contains lactose monohydrate

Mixanval contains lactose monohydrate (a type of sugar). Patients with the rare hereditary conditions of lactose intolerance should not take **Mixanval**.

3. How to take Mixanval

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

Always take **Mixanval** exactly as your doctor has told you. Check with your doctor or pharmacist or nurse if you are not sure.

Swallow your tablet with a glass of water, preferably at the same time each day, in the morning, before breakfast. Your doctor will decide on the correct dose for you. This will normally be one tablet per day.

If you have the impression that the effect of **Mixanval** is too strong or too weak, talk to your doctor or your pharmacist.

Mixanval will usually be prescribed for patients already taking perindopril and amlodipine from separate tablets.

Use in children and adolescents

Use in children and adolescents is not recommended.

If you take more Mixanval than you should

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

If you take too many tablets, the most likely effect in case of overdose is low blood pressure which can make you feel dizzy or faint. If this happens, lying down with your legs raised can help.

If you forget to take Mixanval

It is important to take your medicine every day as regular treatment works better. However, if you forget to take a dose of **Mixanval**, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Mixanval

As the treatment with **Mixanval** is usually life-long, you should discuss with your doctor before you stop taking your tablets.

If you have any further questions on the use of **Mixanval**, ask your doctor or pharmacist.

4. Possible side effects

Mixanval can have side effects.

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

If you experience any of the following, stop taking **Mixanval** and tell your doctor immediately or go to the casualty department of your nearest hospital:

- sudden wheeziness, chest pain, shortness of breath, or difficulty in breathing
- swelling of eyelids, face or lips
- swelling of tongue or and throat, which causes great difficulty in breathing
- severe skin reactions including 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, Toxic Epidermal Necrolysis) or other allergic reactions
- severe dizziness or fainting
- heart attack, unusual fast or abnormal heartbeat
- inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell.

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

The following common side effects have been reported. If any of these cause you problems or if they last for more than one week, you should contact your doctor.

Frequent side effects:

Oedema (fluid retention), headache, dizziness, sleepiness, (especially at the beginning of treatment), vertigo, numbness or tingling sensation in your limbs, vision disturbances (including double vision), tinnitus (sensation of ringing noises in the ears), palpitations (awareness of your heartbeat), flushing, light-headedness due to low blood pressure, cough, shortness of breath, nausea (feeling sick), vomiting (being sick), abdominal pain, taste disturbances, dyspepsia or difficulty of digestion, change in bowel habits, diarrhoea, constipation, allergic reactions (such as skin rashes, itching), muscle cramps, tiredness, weakness, ankle swelling (peripheral oedema).

Other side effects that have been reported include the following list. If any of these get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Less frequent side effects:

- Mood swings, anxiety, depression, sleeplessness, sleep disturbances, trembling, fainting, loss of pain sensation, irregular heartbeat, rhinitis (blocked or runny nose), hair loss, red patches on skin; skin discolouration, back pain, joint pain (arthralgia), muscle pain (myalgia), chest pain, disorder in passing urine, increased need to urinate at night, increased number of times of passing urine, pain, feeling unwell, bronchospasm (tightening of the chest, wheezing and shortness of breath), dry mouth, angioedema (symptoms such as wheezing, swelling of the face or tongue), formation of blister clusters over the skin, kidney problems, impotence, increased sweating, an excess of eosinophils (a type of white blood cells), discomfort

or enlargement of the breasts in men, weight increase or decrease, tachycardia, vasculitis (inflammation of blood vessels), photosensitivity reaction (increased sensitivity of the skin to sun), fever, fall, change in laboratory parameters: high blood

level of potassium reversible on discontinuation, low level of sodium, hypoglycaemia (very low blood sugar level) in case of diabetic patients, increased blood urea, and increased blood creatinine.

- Confusion, psoriasis worsening, changes in laboratory parameters : increased level of liver enzymes, high level of serum bilirubin, cardiovascular disorders (angina, heart attack and stroke), eosinophilic pneumonia (a rare type of pneumonia), swelling of eyelids, face or lips, swelling of the tongue and throat, which causes great difficulty in breathing, severe skin reactions including 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), erythema multiforme (a skin rash which often starts with red itchy patches on your face, arms or legs), sensitivity to light, disorders of the blood such as a lower number of white and red blood cells, lower haemoglobin, lower number of blood platelets, disorders of the blood, inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell, acute renal failure, abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests, abdominal bloating (gastritis), disorder of the nerves which can cause weakness, tingling or numbness, increased muscle tension, swelling of the gums, excess sugar in blood (hyperglycaemia), trembling, rigid posture, mask-like face, slow movements and a shuffling, unbalanced walk discolouration, numbness and pain in fingers or toes (Raynaud’s phenomenon).
- Concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion can occur with ACE-inhibitors. If you have these symptoms contact your doctor as soon as possible.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via **the "6.04 Adverse Drug Reaction Reporting Form"** found online under SAHPRA's publications https//www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of **Mixanval.**

5. How to store Mixanval

Keep all medicine out of the reach of children.

Store at or below 30 °C.

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

Do not store in bathrooms.

Do not use after the expiry date on the bottle.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets).

Store in the original package.

6. Contents of the pack and other information

What Mixanval contains

The active substances are:

Mixanval 5 mg / 5 mg: one tablet contains 5 mg perindopril arginine and 5 mg amlodipine (as amlodipine besilate).

Mixanval 5 mg / 10 mg: one tablet contains 5 mg perindopril arginine and 10 mg amlodipine (as amlodipine besilate).

Mixanval 10 mg / 5 mg: one tablet contains 10 mg perindopril arginine and 5 mg amlodipine (as amlodipine besilate).

Mixanval 10 mg / 10 mg: one tablet contains 10 mg perindopril arginine and 10 mg amlodipine (as amlodipine besilate).

The other ingredients in the tablet are: colloidal anhydrous silica, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

Contains sugar (lactose) 65,23 mg for 5/5; 135,47 mg for 5/10 mg; 137,40 mg for 10/5 mg and 130,47 mg for 10/10 mg.

What Mixanval looks like and contents of the pack

Mixanval 5 mg/5 mg tablets:

White, rod-shaped tablet engraved with 5/5 on one face and  on the other face.

Mixanval 5 mg/10 mg tablets:

White, square-shaped tablet engraved with 5/10 on one face and  on the other face.

Mixanval 10 mg/5 mg tablets:

White, triangular-shaped tablet engraved with 10/5 on one face and on the other face.

Mixanval 10/10 mg tablets:

White, round tablet engraved with 10/10 on one face and on the other face.

A white polypropylene container equipped with a low-density polyethylene flow reducer and a low density white polyethylene stopper containing desiccant gel, with 30 tablets placed in an outer carton.

Holder of certificate of registration

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