PATIENT INFORMATION LEAFLET

WARNING: If you are taking ZATONAV with some medicines used to treat allergies, medicines used to relieve anxiety and/or trouble sleeping, medicines used to correct irregular heartbeat and medicines used to treat migraine headache they may cause serious adverse events.

SCHEDULING STATUS: S4

ZATONAV film-coated tablets

Atazanavir 300 mg/ Ritonavir 100 mg

Contains sugar: Lactose monohydrate 166,8 mg, sorbitol 100,0 mg.

Read all of this leaflet carefully before you start taking ZATONAV.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- ZATONAV 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 contained in this leaflet

1. What ZATONAV is and what it is used for
2. What you need to know before you take ZATONAV
3. How to take ZATONAV
4. Possible side effects
5. How to store ZATONAV
6. Contents of the pack and other information

1. What ZATONAV is and what it is used for

ZATONAV contains two active ingredients. The main active ingredient is atazanavir, which belongs to

a class of antiviral medicines called protease inhibitors. ZATONAV also contains ritonavir, which is also a protease inhibitor, and which is used together with atazanavir to increase its effectiveness.

Your doctor has prescribed ZATONAV to you to treat your Human Immunodeficiency Virus (HIV) infection. ZATONAV is used in combination with other antiretroviral medicines for the treatment of your HIV infection.

2. What you need to know before you take ZATONAV

Do not take ZATONAV:

- If you previously suffered an allergic reaction to any of the active ingredients, atazanavir or ritonavir, or any other ingredient of ZATONAV (listed in section 6).
- If you are taking any other medicines containing ritonavir or atazanavir.
- If you have a liver disorder.
- If you are pregnant or breastfeeding your baby.
- If you are an elderly (age 65 years or more), as safety and efficacy have not been established.
- If you are currently taking any of the following medicines:
  - Amiodarone, encainide, flecainide, propafenone, quinidine, bepridil and digoxin (for treatment of irregular heartbeats and/or heart failure).
  - Loratadine (used to treat hay fever and other allergies).
  - Metoclopramide (used to treat heartburn).
  - Ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat migraines and headaches).
  - Fluticasone or budesonide (inhaled or nasal corticosteroids).
  - Fusidic acid (an antibiotic).
  - Lovastatin and simvastatin (used for lowering cholesterol).
  - Nevirapine, efavirenz, indinavir, saquinavir, didanosine and tenofovir (for treatment of aids).
  - Oral contraceptives.
  - Pimozide and clozapine (used to treat certain mental conditions).
  - Irinotecan (for treatment of cancer).
  - Protease inhibitor indinavir.

- Rifabutin, rifampicin (antimycobacterial).
- St John's Wort (Hypericum perforatum) (a herbal remedy used for depression and anxiety).
- Midazolam taken by mouth or parenterally, triazolam, clorazepate, diazepam, estazolam, flurazepam (used to help you sleep and/or to relieve anxiety).
- Voriconazole (used to treat fungal infections).

If you are takin any of these medicines, tell your doctor immediately. Taking these medicines with ZATONAV could cause serious side effects or stop these medicines from working properly.

Warnings and precautions

Take special care with ZATONAV:

- If you are taking ZATONAV you may still develop infections or other illnesses associated with HIV disease and AIDS. It is therefore important that you remain under the supervision of your doctor while taking ZATONAV.
- If you have or had a history of liver disorders, as patients with a history of liver disease, including chronic hepatitis B or C, are at increased risk of severe and potentially fatal liver side effects. Your doctor will carefully consider the best treatment for you and may conduct blood tests to monitor your liver function.
- If you have haemophilia type A and B, as ZATONAV might increase the risk of bleeding.
- Combination antiretroviral therapy (including ZATONAV) may change your body shape, by changing the way body fat is distributed. You may lose fat from your legs, arms and face; gain fat around the tummy (abdomen) and internal organs; get larger breasts or fatty lumps on the back of the neck ("buffalo hump").
- If you have or have had diabetes, as increased blood sugar has been reported in patients receiving ZATONAV. If you experience thirst, frequent urination, blurred vision or weight loss, this may indicate raised sugar levels in the blood.
- If you have bone problems, including previous bone breaks (fractures).
- Some patients with HIV taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms, tell your doctor.

- If you experience symptoms of dizziness, light-headedness, fainting or sensation of abnormal heartbeats. ZATONAV may cause changes in your heart rhythm and the electrical activity of your heart. These changes may be seen on an ECG (electrocardiogram).
- If you have advanced HIV infection and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. Common examples of opportunistic infections are tuberculosis (cough that does not go away, weight loss, sweating a lot at night), *pneumocystis jirovecii* pneumonia (rapid breathing, shortness of breath), atypical mycobacterial infection (progressively severe diarrhoea, stomach pain, nausea and vomiting), cytomegalovirus retinitis (unclear vision, blind spot, specks in your vision) and cryptococcal meningitis (headache, mentalchanges including confusion, sensitivity to light, nausea, vomiting).
- In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking antiretroviral medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to get the necessary treatment.
- If you develop a rash after you started taking ZATONAV, please inform your doctor immediately, as you may have to stop the treatment.
- ZATONAV will not cure or prevent HIV infection or AIDS, however, it helps keep HIV from reproducing and appears to slow down the destruction of the immune system. **ZATONAV will not keep you from spreading HIV to other people.**

Other medicines and ZATONAV

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicines).

It is important for you to tell your doctor if you are taking any of the following medicines:

- Antibiotic medicines (e.g. rifabutin, clarithromycin, erythromycin, ethionamide, rifampin, rifampicin).
- Anticancer medicines (e.g. cyclophosphamide, daunorubicin, doxorubicin, etoposide, ifosfamide, nilotinib, paclitaxel, tamoxifen, vincristine, vinblastine).
- Anti-emetic medicines (e.g. cisapride, dronabinol, ondansetron, prochlorperazine, metoclopramide).
- Anti-epilepsy medicines (e.g. carbamazepine, phenytoin, phenobarbitone).
- Antifungal medicines (e.g. fluconazole, ketoconazole, itraconazole, miconazole, voriconazole).
- Antihistamine medicines (e.g. loratadine).
- Anti-infective medicines (e.g. atovaquone, sulfamethoxazole/ trimethoprim).
- Antineoplastic medicines (e.g. irinotecan).
- Antiretroviral medicines (e.g. delavirdine, didanosine, efavirenz, maraviroc, nevirapine, zidovudine, amprenavir, indinavir, nelfinavir, saquinavir, tenofovir).
- Blood vessel dilating (vasodilator) medicines (pentoxifylline).
- High blood pressure medicines (e.g. doxazosin, losartan, prazosin, tadalafil, terazosin).
- Medicines that prevent the formation of blood clots (e.g. warfarin).
- Medicines such as fusidic acid used for long-term treatment of infections of the bones and joints (e.g. osteomyelitis).
- Cholesterol lowering medicines (e.g. atorvastatin, fluvastatin, lovastatin, pravastatin or simvastatin).
- Medicines to treat epilepsy, seizures, fits (e.g. carbamazepine, clonazepam, valproate, ethosuximide, phenobarbital, phenytoin).
- Medicines to treat depression (e.g. amitriptyline, bupropion, clomipramine, desipramine, doxepin, fluoxetine, fluvoxamine, imipramine, maprotiline, nefazodone, nortriptyline, paroxetine, sertraline, trazodone, trimipramine, venlafaxine).
- Medicines to treat diarrhoea (e.g. diphenoxylate, loperamide).
- Medicines for treatment of migraines and headaches (e.g. bromocriptine, dihydroergotamine, ergonovine, methylergonovine, methysergide).
- Medicines to treat parasites (e.g. albendazole, atovaquone, chloroquine, metronidazole, primaquine, proguanil, pyrimethamine, quinine, trimetrexate).

- Antipsychotic/neuroleptic medicines (e.g. clozapine, haloperidol, pimozide, risperidone, thioridazine).
- Medicines for erectile dysfunction (e.g. sildenafil, tadalafil, vardenafil).
- Medicines to treat certain heart conditions (e.g. amiodarone, amlodipine, bepridil, betaxolol, digoxin, diltiazem, disopyramide, encainide, felodipine, flecainide, isradipine, systemic lidocaine, metoprolol, mexiletine, nifedipine, nicardipine, nimodipine, nisoldipine, nitrendipine, penbutolol, pindolol, propafenone, propranolol, quinidine, timolol, tocainide, verapamil).
- Herbal products for anxiety and depression, such as St John's Wort (Hypericum perforatum).
- Medicines affecting the immune system (e.g. ciclosporin, sirolimus (rapamycin), tacrolimus).
- Medicines to treat asthma and other lung-related problems (e.g. theophylline).
- Oral contraceptives or using a patch contraceptive to prevent pregnancy (e.g. ethinyl oestradiol and norethindrone).
- Pain medicines (e.g. alfentanil, codeine, diclofenac, fentanyl, flurbiprofen, hydrocodone, hydromorphone, ibuprofen, indomethacin, ketoprofen, ketorolac, levomethadyl, meperidine, methadone, morphine, nabumetone, naproxen, oxycodone, pethidine, piroxicam, propoxyphene, sulindac, tramadol).
- Sedative/hypnotic medicines (e.g. alprazolam, buspirone, clorazepate, diazepam, estazolam, flurazepam, lorazepam, oral and parenteral midazolam, oxazepam, propofol, temazepam, triazolam, zolpidem).
- Steroid medicines (e.g. budesonide, dexamethasone, fluticasone propionate).
- Stomach ulcer, acid reducing medicines (e.g. cisapride, famotidine, lansoprazole, proguanil, pyrimethamine, omeprazole).

ZATONAV with food and drink:

You can take ZATONAV with or without food.

Pregnancy, breastfeeding and fertility

You must not take ZATONAV if you are pregnant or breastfeeding your baby.

If you are pregnant or breastfeeding your baby, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before you start taking ZATONAV.

Driving and using machines

ZATONAV may affect your ability to drive and use machines. You should not drive and use machines until you know how ZATONAV affects you.

ZATONAV may cause dizziness, sleepiness, disorientation, blurred vision, and fainting (syncope).

Important information about some of the ingredients of ZATONAV tablets:

ZATONAV tablets contain lactose and sorbitol which may have an effect on the control of your blood sugar if you have diabetes mellitus.

ZATONAV contains lactose. Patients with the rare hereditary conditions of lactose or galactose intolerance (e.g. galactosaemia) should not take ZATONAV.

ZATONAV contains sorbitol, which may cause diarrhoea. Patients with the rare hereditary condition of sorbitol intolerance should not take ZATONAV.

3. How to take ZATONAV

Do not share medicines prescribed for you with any other person. Always take ZATONAV exactly as your doctor has told you.

Check with your doctor or pharmacist if you are not sure.

Adults: The recommended dose of ZATONAV is one tablet once daily taken with food. The ZATONAV tablets should be swallowed whole.

Your doctor will tell you how long your treatment with ZATONAV will last.

Do not suddenly stop taking ZATONAV without consulting with your doctor first.

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

If you take more ZATONAV than you should:

In the event of overdosage, speak to a doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre for help.

If you forget to take ZATONAV:

If you forget to take a dose of ZATONAV, take it as soon as you remember and then continue as before. Do not take a double dose to make up for missed individual doses.

Effects when treatment with ZATONAV is stopped:

If you have stopped taking ZATONAV for any reason, especially if you think you are having side effects, or for another illness, it is important that you contact your doctor before restarting. In some cases your doctor will ask you to restart ZATONAV under direct medical supervision or where medical care can be easily accessed by yourself or others. If your doctor thinks that there is a possibility your symptoms were related to a hypersensitivity reaction, you may be told not to take ZATONAV or any other medicine containing atazanavir and ritonavir ever again.

4. Possible side effects

ZATONAV can have side effects.

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

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

- A life-threatening allergic reaction referred to as anaphylaxis. Symptoms include, but are not limited to, fast or irregular breathing, puffiness or swelling around the face, shortness of breath, a sudden severe decrease in blood pressure, abdominal pain and cramping, anxiety, confusion, cough, diarrhoea, difficulty in swallowing, fainting, light-headedness, dizziness, hives, itchiness, wheezing and blocked nose.
- Severe skin rash,

OR

If you experience any one or more symptoms affecting at least TWO organ systems (e.g. shortness of breath (respiratory system) and diarrhoea (gastrointestinal system), stop taking ZATONAV and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Respiratory – shortness of breath, sore throat or cough, swelling of the face, tongue or throat and difficulty with breathing.
- Gastrointestinal – nausea or vomiting or diarrhoea or abdominal (stomach) pain.
- Musculoskeletal – severe tiredness or aches and pains or generally feeling ill.

These are all very serious side effects. If you have them, you may have had a serious reaction to

ZATONAV. 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:

- If your heart beats harder (increased intensity), or you experience other disorders such as an increase in your heart rate, an irregular heartbeat or a heart attack.
- Low blood pressure.
- Fever.
- Headache.

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:

- Headache, dizziness.
- Vomiting, diarrhoea, abdominal pain, nausea, indigestion, yellowing of the skin and white part of the eyes indicating liver inflammation.
- Rash, itching.
- Accumulation or loss of body fat (body changes due to fat redistribution).
- Loss of appetite, increased appetite, weight loss.
- Anxiety.
- Numbness, tingling, a burning sensation or weakness of hands and feet.
- Fainting, swelling of feet and lower legs.
- Bad taste in the mouth, loss of taste, prickling sensation around or near the mouth, swelling of the face.
- Widening of the blood vessel.
- Cough or hoarseness.
- Mouth ulcers, dry mouth, sore throat.
- Inflammation of the pancreas, inflammation of the stomach, enlarged abdomen (excessive amount of air or gas in the stomach), bloated feeling.
- Eczema and Stevens-Johnson syndrome: an extremely severe skin reaction with ulcers or blisters on the skin, acne, dry skin and other skin disorders, inflammation of the hair follicles, severe

tiredness, chest pain, feeling of bodily discomfort (malaise) and weakness, fever or chills.

Less frequent side effects:

- Weight gain, excess of watery fluid collecting in the tissues of the body.
- Depression, disorientation, sleep disorders, confusion.
- Abnormal dreams, forgetfulness, feeling nervous, emotional instability.
- Exaggerated feeling of physical and mental well-being, seeing or hearing things that are not there, abnormal thinking, sleepiness.
- Enlargement of the liver and spleen, formation of gallstones; stop of the flow of bile, inflammation of the gallbladder.
- Hair loss.
- Anaemia (a low red blood cell count), that can leave you feeling tired and lethargic, blood under the skin.
- A rash of round, red weals on the skin which itch intensely.
- Increased sensitivity of the skin to sunlight, psoriasis, dandruff.
- Kidney pain and other kidney disorders, blood in the urine, protein in the urine, frequent passing of urine, difficulty in passing urine, kidney stones.
- Kidney failure; passing excessive urine at night.
- Acute kidney disorders as well as failure.
- Impotence, breast enlargement in men, penis disorder, decreased sexual drive.
- Disease of the lymph nodes, dehydration.
- Diabetes (body cannot remove sugar from the blood normally).
- Deficiency of vitamins in the diet; general ill health and malnutrition.
- Swelling of feet and lower legs.
- Feeling agitated, personality disorder.
- Breathing difficulties, lung disorders.
- An abnormal sensation such as prickling or burning, increased sensitivity or abnormal feeling to touch, abnormal sensation in arms or legs.
- Seizure (fits), speech disorder, incoordination, nerve pain.
- Disturbance of nervous system, paralysis, abnormal sense of smell.

- Trembling, bleeding.
- Abnormal vision, blurred vision, double vision, eye pain, inflammation of parts of the eye and the eyelid, abnormal intolerance of light.
- Hearing disorder, increased wax in the ear, ringing in the ears, sensation of movement.
- Severe tummy pain (possible inflammation of your pancreas).
- Runny nose, bleeding nose, hiccup; sweating.
- Breakdown of muscle tissue and muscle disorders.
- Back pain; joint disorders, neck pain or stiffness, twitching.
- Muscle pain, cramps or weakness.
- Abnormal laboratory test results (this will be discussed with you by your doctor).

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 "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 ZATONAV.

5. How to store ZATONAV

Store all medicines out of reach of children.

Store at or below 30 °C.

Store the tablets in the original container.

Do not remove from the carton until required for use.

Keep the bottle tightly closed.

Do not store in bathrooms.

Do not use after the expiry date stated on the label.

Return all unused medicine to your pharmacist.

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

6. Contents of the pack and other information

What ZATONAV contains

The active substances are atazanavir and ritonavir.

Each ZATONAV film-coated tablet contains 300 mg of atazanavir co-formulated with 100 mg of ritonavir as a pharmacokinetic enhancer.

Contains: Lactose monohydrate (sugar) 166,8 mg, sorbitol 100,0 mg.

The other ingredients are colloidal silicon dioxide, copovidone, crospovidone, magnesium stearate, maize starch, microcrystalline cellulose, sodium chloride, sodium stearyl fumarate, sorbitan monolaurate, film-coat (hypromellose, macrogol).

What ZATONAV looks like and contents of the pack

A bi-layered, film-coated, capsule shaped, biconvex tablet having one layer plain with pale yellow to yellow colour and a white to off-white layer debossed with ‘M777’.

ZATONAV are presented in the following:

High density polyethylene (HDPE) bottle pack (marketable pack) comprises of white coloured HDPE bottle with white opaque polypropylene (PP) screw cap.

High density polyethylene (HDPE) bottle pack (marketable pack) comprises of white coloured HDPE bottle (pill jar) with white opaque polypropylene (PP) tamper evident closure with inbuilt plastic canister silica gel desiccant.

Pack size of 30’s.

Holder of Certificate of Registration

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