PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

PRETAMYL Tablets

Pretomanid

Contains sugar: Lactose monohydrate 294,4 mg and 5 mg sodium per tablet

Read all of this leaflet carefully before you start taking PRETAMYL

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

1. What PRETAMYL is and what it is used for

PRETAMYL contains the active substance pretomanid.

PRETAMYL is for use only as part of a combination antimycobacterial regimen that includes pretomanid, bedaquiline, and linezolid.

What is the combination regimen of pretomanid tablets, bedaquiline, and linezolid?

PRETAMYL is a prescription medicine used as part of a combination regimen with bedaquiline and

linezolid. The combination regimen of PRETAMYL, bedaquiline, and linezolid includes three prescription antibiotics that are used together in adults to treat tuberculosis (TB) of the lungs that is extensively drug resistant (XDR) or who cannot tolerate or do not respond to treatment for multidrug-resistant (MDR) TB.

PRETAMYL is not for use in people who have:

- TB that is not resistant to antibiotics.
- An inactive (latent) TB infection.
- A type of TB other than TB of the lungs.
- MDR TB who can tolerate or who respond to medicines usually used to treat MDR TB.

It is not known if PRETAMYL is safe and effective for use except in combination with bedaquiline and linezolid as part of the recommended dosing regimen.

It is not known if PRETAMYL is safe and effective in children.

2. What you need to know before you take PRETAMYL

Do not take PRETAMYL:

- If you are allergic (hypersensitive) to pretomanid, bedaquiline, linezolid or any other ingredients of PRETAMYL (listed in section 6).
- If you are not allowed to take bedaquiline and/or linezolid. Please also refer to the individual patient information leaflets for these products.
- If you are using rifampicin (antibiotic used to treat several types of bacterial infections including tuberculosis) or efavirenz (antiretroviral drug used to treat human immunodeficiency disease).
- If you are pregnant or breastfeeding your baby (see section 4.6).

Warnings and precautions

Take special care with PRETAMYL:

- If you have liver problems.
- If you have kidney problems.
- If you drink alcohol on a regular basis.
- If you have a decrease in bone marrow activity resulting in a reduction in red blood cell production (myelosuppression), or a decrease in the haemoglobin concentration within red blood cells

(anaemia).

- If you have a reduced number of white blood cells (leukopenia).
- If you have a deficiency of platelets in the blood (thrombocytopenia).
- If you have weakness, numbness and pain in your arms, hands, legs and feet as a result of nerve damage (peripheral neuropathy).
- If you experience loss of vision or colours appearing subtly washed out due to damage to the optic nerve (optic neuropathy).
- If you have or have had an abnormal heart rhythm (ECG) or other heart problems, including heart failure.
- If you have a family history of a heart problem called "congenital long QT syndrome."
- If you have decreased thyroid gland function (hypothyroidism).
- If you have been told that you have low levels of calcium, magnesium or potassium in your blood.
- If you suffer from a condition where the body produces too much lactic acid (lactic acidosis). Contact your doctor if you have recurrent nausea or vomiting.
- If you are pregnant or plan to become pregnant It is not known if pretomanid will harm your unborn baby. Talk to your healthcare provider about the possible risks to your baby if you take the combination regimen of PRETAMYL, bedaquiline, and linezolid while you are pregnant.
- If you are breastfeeding or plan to breastfeed. It is not known if pretomanid passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take the combination regimen of PRETAMYL, bedaquiline, and linezolid.
- If you have the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
- If you have liver damage: There is a risk of liver damage when you are treated with PRETAMYL, linezolid and bedaquiline. Therefore, your doctor will monitor signs of liver damage and take blood samples before initiating treatment.

Tell your doctor if you experience the following symptoms:

- Fatigue (feeling tired).
- Anorexia (when you have a low weight and have a fear of gaining weight).
- Nausea.

- Yellowing of the skin and eyes.
- Dark urine.
- Abdominal pain.

Children and adolescents under 18 years of age

Safety and effectiveness of PRETAMYL in paediatric patients have not been established.

Other medicines and PRETAMYL

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

You should not take herbal products or medicines that can harm your liver during treatment with the combination regimen of PRETAMYL, bedaquiline, and linezolid.

The combination regimen of PRETAMYL, bedaquiline, and linezolid regimen may affect how other medicines work, and other medicines may affect how the combination regimen of PRETAMYL, bedaquiline, and linezolid works.

Especially tell your healthcare provider if you take:

- A type of medicine called a CYP3A4 inducer used to treat tuberculosis or certain other infections, such as efavirenz or rifampicin. Ask your healthcare provider if you are not sure.
- Lopinavir/ Ritonavir (medicines used to treat HIV infection).
- Midazolam (medicines used to help you sleep).
- Methotrexate (a medicines used to treat severe joint inflammation, cancer and the skin disease psoriasis).
- Ciprofloxacin (antibiotic medicines used to treat bacterial infections).
- Indomethacin (a medicine used to treat pain and inflammation).
- Valsartan and statins (medicines used to lower your cholesterol).
- Digoxin (medicines used to treat heart conditions).
- Verapamil (medicine used to treat high blood pressure).
- Medicines used to treat and prevent blood clots and a stroke (dabigatran etexilate).
- Medicines used to treat type 2 diabetics such as glyburide.
- Sulfasalazine (medicines used to treat rheumatoid arthritis and inflammation).

PRETAMYL with food and drink and alcohol

PRETAMYL should be taken with meals.

You should not drink alcohol while taking the combination regimen PRETAMYL, bedaquiline, and linezolid.

Pregnancy and breastfeeding and fertility

If you are pregnant or breastfeeding your baby while taking PRETAMYL, please consult your doctor, pharmacist or other healthcare professional for advice before taking PRETAMYL.

You should not take PRETAMYL if you are pregnant or breastfeeding.

Driving and using machinery

PRETAMYL may have a minor influence on the ability to drive and use machines. PRETAMYL may cause dizziness and visual impairment. You should not operate hazardous machinery, including motor vehicles until you know how PRETAMYL affects you.

Important information about some of the ingredients of PRETAMYL

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

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

PRETAMYL contains sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

3. How to take PRETAMYL

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

PRETAMYL must only be taken with bedaquiline and linezolid as part of the dosing regimen prescribed by your healthcare provider.

Take the combination regimen of PRETAMYL, bedaquiline, and linezolid exactly as your healthcare provider tells you to take it.

It is important that you complete the full course of treatment with the combination regimen of PRETAMYL, bedaquiline, and linezolid, and not miss any doses, even if you feel better before you have completed the full course of treatment. Missing doses may decrease the effectiveness of the treatment and increase the chance that your TB will not be treatable by the combination regimen of PRETAMYL,

bedaquiline, and linezolid or other medicines.

Take the combination regimen of PRETAMYL, bedaquiline and linezolid for a total of 26 weeks. Your healthcare provider will tell you if you should take the combination regimen of PRETAMYL, bedaquiline, and linezolid for longer than 26 weeks. Your healthcare provider will tell you if you should stop taking linezolid before you have taken it for 26 weeks or if you should reduce your dose of linezolid due to side effects.

Your healthcare provider or caregiver will watch you take your doses of PRETAMYL, bedaquiline, and linezolid. PRETAMYL, bedaquiline, and linezolid can be taken together. Swallow PRETAMYL whole with water. Take PRETAMYL, bedaquiline, and linezolid with food.

Week 1 and Week 2:

Take 200 mg of PRETAMYL (1 tablet), 400 mg of bedaquiline, and 1,200 mg of linezolid **1 time each day.**

Week 3 to Week 26:

Take 200 mg of PRETAMYL (1 tablet) and 1,200 mg of linezolid **1 time each day.**

Take 200 mg of bedaquiline **3 times a week.**

Take your doses of bedaquiline at least 48 hours apart. For example, you may take bedaquiline on Monday, Wednesday, and Friday every week from Week 3 to Week 26.

You may need to take the combination regimen of PRETAMYL, bedaquiline, and linezolid for longer than 26 weeks. Talk with your healthcare provider.

If you have the impression that the effect of PRETAMYL is too strong or too weak, tell your doctor or pharmacist.

If you take more PRETAMYL than you should

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

If you forget to take or missed a dose of PRETAMYL

If you miss a dose of PRETAMYL, or do not complete the total 26 weeks of treatment, your treatment may not work as well, and your TB may be harder to treat. If your healthcare provider tells you to stop taking the combination regimen of PRETAMYL, bedaquiline, and linezolid for a period of time, follow the instructions given to you by your healthcare provider for taking the missed doses at the end of your

treatment. You should not make up any missed doses of linezolid alone that your healthcare provider told you not to take due to side effects.

Effect when treatment with PRETAMYL is stopped

Do not stop taking PRETAMYL, bedaquiline, or linezolid without first talking to your healthcare provider.

4. Possible side effects

PRETAMYL can have side effects.

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

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

- Swelling of the hands, feet, ankles, face, lips, tongue and mouth or throat, which may cause difficulty in swallowing or breathing.

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

Liver problems

Your healthcare provider should do blood tests to check your liver at least before you start taking the combination regimen of PRETAMYL, bedaquiline, and linezolid, 2 weeks after starting treatment, and then monthly during treatment .Tell your healthcare provider right away if you have symptoms of liver problems, such as: unusual tiredness, loss of appetite, nausea, yellowing of your skin or the whites of your eyes, dark (tea-coloured) urine, tenderness in the upper right side of stomach-area (abdomen).

Low blood cell counts

The combination regimen of PRETAMYL, bedaquiline, and linezolid can cause low red blood cell counts (anaemia), low white blood cell counts (leukopenia), low blood platelet counts (thrombocytopenia) or a combination of low red and white blood cell counts and low blood platelet counts (pancytopenia). Low blood cell counts are a side effect of linezolid. Anaemia is a common side effect of linezolid but can be

serious and life-threatening. Low blood cell counts were reversible when linezolid treatment was reduced, stopped for a period of time, or stopped permanently. Your healthcare provider should check your blood cell counts at least before you start taking the combination regimen of PRETAMYL, bedaquiline, and linezolid, 2 weeks after starting treatment, and then monthly during treatment.

Nerve problems in your arms, hands, legs, and feet (peripheral neuropathy)

The combination regimen of PRETAMYL, bedaquiline, and linezolid can cause nerve problems in your arms, hands, legs, and feet. Tell your healthcare provider if you have symptoms of nerve problems in your arms, hands, legs, or feet, including numbness, burning, a feeling of "pins and needles", tremors, problems with balance, weakness.

Nerve problems in your arms, hands, legs, feet, and eyes are common side effects of long-term use of linezolid but can be serious. Nerve problems caused by linezolid were generally reversible or improved when symptoms of nerve problems were monitored by the healthcare provider and linezolid treatment was reduced, stopped for a period of time, or stopped permanently.

Vision problems

The combination regimen of PRETAMYL, bedaquiline, and linezolid can cause nerve problems in your eyes (optic neuropathy). Nerve problems in your eyes can cause problems with your vision. **Tell your healthcare provider right away** if you have symptoms of nerve problems in your eyes, such as changes in vision.

Heart rhythm problem called QT prolongation

The combination regimen of PRETAMYL, bedaquiline, and linezolid can cause a heart rhythm problem. Heart rhythm problem is a side effect of bedaquiline. Your healthcare provider should do a test called an electrocardiogram (ECG) to check your heart before you start taking the combination regimen of PRETAMYL, bedaquiline, and linezolid and at least 2, 12, and 24 weeks after starting treatment. Tell your healthcare provider right away if you have a change in heartbeat (a fast or irregular heartbeat) or feel dizzy or faint.

Effects on male fertility

It is not known if pretomanid can cause fertility problems in males. This could affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

Build-up of an acid in your blood (lactic acidosis)

The combination regimen of PRETAMYL, bedaquiline, and linezolid can cause a build-up of acid in your blood. A build-up of acid in your blood is a side effect of linezolid.

Call your healthcare provider right away if you have nausea and vomiting that keep coming back.

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 reported:

- Acne.
- Nausea.
- Vomiting.
- Muscle and bone pain.
- Insomnia.
- Distortion of the sense of taste (dysgeusia).
- Dizziness.
- Visual impairment.
- Eye irritation.
- Eye pain.
- Headache.
- Abnormal blood tests that may be due to injury to your liver.
- Heartburn.
- Indigestion (dyspepsia).
- Constipation.
- Decreased appetite.
- Rash.
- Itching.
- Dry skin.
- Hair loss (alopecia).
- Stomach pain.
- Chest pain that worsens when you breathe or cough.
- Lower respiratory tract infection.

- Abnormal blood tests that may be due to injury to your pancreas.
- Coughing up blood.
- Coughing.
- Low blood sugar.
- Unusual weight loss.
- Fatigue.
- Weakness.
- Diarrhoea.

Less frequent side effects reported:

- Fungal infections in mouth or throat which appear as white patches.
- Lack of white or red blood cells.
- Increased acidity of your blood.
- Too much fluid loss in your body.
- Low calcium or magnesium levels in your blood.
- Low blood volume.
- Anxiety or depression.
- Eye lens disorders, dry eyes, itching and swelling of the eyes.
- Deafness.
- Feeling of increased heartbeat.
- Low blood pressure.
- Cough and nosebleed.
- Feeling bloated.
- Burning tongue and small structures present on the tongue.
- Taste disorder.
- Enlarged liver.
- Yellowing of the skin and or eyes.
- Skin rash caused by an allergic reaction.
- Darkening of an area of the skin (hyperpigmentation).
- Muscles and skeleton stiffness.

- Seizures.
- Inability to have or maintain an erection.
- Feeling unwell.
- Low concentration of sodium in your body.
- High or low concentration of potassium in your body.
- High blood sugar level in your body.
- Abnormal presence of the protein albumin in the urine.
- Increased blood levels (creatinine and phosphokinase, and uric acid).

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 or pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem 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 PRETAMYL.

How to store PRETAMYL

Store all medicines out of reach of children.

Store at or below 30 °C.

Keep in original container and keep container tightly closed.

Do not store in a bathroom.

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

Return all unused medicine to your pharmacist.

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

Contents of the pack and other information

What PRETAMYL contains

The active ingredient is pretomanid.

Each PRETAMYL tablet contains 200 mg pretomanid.

Contains sugar: Lactose monohydrate 294,4 mg per tablet.

The other ingredients are colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate.

What PRETAMYL looks like and contents of the pack

White to off-white oval tablets debossed with M on one side and P200 on the other side.

Contents of the pack

PRETAMYL is packaged in an HDPE bottle pack (marketable pack) comprised of round wide mouth white high-density polyethylene (HDPE) bottle with white opaque polypropylene screw cap with aluminium induction sealing liner wad with absorbent cotton. Pack sizes: Bottles of 28 and 30 tablets.

PRETAMYL is packaged in either white, round, high-density polyethylene bottles with white polypropylene child-resistant closure or child-resistant blister packages comprised of a polyvinylchloride film with foil and paper backing. Pack sizes: Bottles of 30 tablets.

Unit dose blister pack of 28 (2 strips of 14 tablets).

Holder of Certificate of Registration

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