PATIENT INFORMATION LEAFLET

SCHEDULING STATUS **S4**

PEFRILO Oral granules

Lopinavir and Ritonavir

Contains sugar: mannitol (583 mg) per sachet.

Read all of this leaflet carefully before you start taking PEFRILO

- 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.
- PEFRILO 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 PEFRILO is and what it is used for

PEFRILO is indicated in combination with other antiretroviral medicines for the treatment of HIV-1 infection in adults and children 6 months and older, weighing over 6 kg. It slows down the spread of infection in your child's body. PEFRILO is an antiretroviral medicine. It belongs to a group of medicines called protease inhibitors.

PEFRILO is prescribed for use in combination with other antiviral medicines. Your health care provider will discuss with you which medicines are best for your child.

This medicine is intended for use in children. Safety information on use in adults is also provided.

2. What you need to know before you give PEFRILO

Do not give PEFRILO:

- if he/she are allergic (hypersensitive) to lopinavir, ritonavir or any of the other ingredients of PEFRILO (listed in section 6).
- if you if your child has severe liver problems
- If your child is taking any of the following medicines:
  - Amiodarone, dronedarone, bepridil, quinidine, propafenone, verapamil (drugs used to treat abnormal heartbeat);
  - Pimozide, lurasidone (used to treat depression);
  - Quetiapine (used to treat schizophrenia, bipolar disorder and major depressive disorder);
  - Astemizole, terfenadine (commonly used to treat allergy symptoms);
  - Triazolam, diazepam, flurazepam (used to relieve anxiety or trouble sleeping);
  - Midazolam taken by mouth and clorazepate (sedative, used to treat

epilepsy);

- Ranolazine (used to treat chronic chest pain [angina]);
- Cisapride (used to relieve certain stomach problems);
- Ergotamine, dihydroergotamine, ergonovine, methylergonovine (used to treat migraine headaches);
- Simvastatin and lovastatin (used to lower blood cholesterol);
- Colchicine (anti-gout medicine) – patients with renal or hepatic impairment. (See the section on Other Medicines and PEFRILO);
- Fusidic acid (used to treat skin infections such as impetigo and infected dermatitis). (See the section on Taking Other Medicines);
- Elbasvir/grazoprevir, ombitasvir/paritaprevir/ritonavir with or without (used to treat chronic hepatitis C virus [HCV]);
- Sildenafil used to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery). Sildenafil used to treat erectile dysfunction may be taken under the health care provider's supervision (see "Warnings and precautions"section);
- Avanafil or vardenafil (used to treat erectile dysfunction);
- Products that contain St John's Wort (Hypericum perforatum).

Read the list of medicines under 'Other medicines and PEFRILO' for information on certain other medicines which require special care.

If your child is taking any of these medicines, ask the health care provider about making changes either in the treatment for your child's other condition(s) or in your child's antiretroviral treatment.

Warnings and precautions

Take special care with PEFRILO:

Check with your health care provider before giving PEFRILO to your child if your child:

- has or had liver disease—patients with chronic hepatitis B or C treated with antiretroviral medicines such as PEFRILO are at an increased risk for severe and potentially fatal liver adverse reactions, and may require blood tests to monitor liver function;
- has haemophilia type A and B (a disorder of blood coagulation)— PEFRILO may increase the risk of bleeding;
- has diabetes—treatment with HIV protease inhibitors like PEFRILO may occasionally cause or aggravate diabetes.

This medicine helps to control HIV infection, but it is not a cure for it. Your child may still develop other infections and other illnesses associated with HIV disease (e.g. opportunistic infections). These require specific and sometimes preventive treatment. You should keep in regular contact with your health care provider. Do not stop your child's medicine without first talking to your health care provider.

Your child can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Discuss with the health care provider the precautions needed to avoid infecting other people.

It is important that the health care provider knows about all your child's symptoms, even when you think they are not related to HIV infection.

Tell the health care provider if your child's blood cholesterol is high. Treatment with PEFRILO may increase blood cholesterol and other blood lipids. Therefore, your child may require blood tests during treatment.

In rare cases, patients receiving lopinavir and ritonavir (contained in PEFRILO) have developed pancreatitis (inflammation of the pancreas). You should contact the health care provider if your child develops symptoms such as abdominal pain, nausea and vomiting, which may be due to pancreatitis.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections, 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 infection that may have been present with no obvious symptoms. If you notice any symptoms of infection, tell the health care provider immediately.

In addition to opportunistic infections, autoimmune disorders (resulting from the immune system attacking healthy body tissue) may also occur after your child starts taking medicines for treating HIV infection. Autoimmune disorders may occur many months after starting 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 in your child, tell the health care provider immediately.

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue). The risk of developing this

disease may be higher, e.g. when the immune system is severely compromised or when drinking alcohol regularly. If you notice joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement, tell the health care provider.

Muscle pain, tenderness or weakness, particularly in combination with these medicines. On rare occasions these muscle disorders have been serious.

On rare occasions PEFRILO may affect the heart rhythm. If your child has or had any heart problems, you should tell the health care provider before giving PEFRILO.

PEFRILO may interact with other medications, which may alter their effects (see also the section above, ‘do not take PEFRILO’, and below ‘Other medicines and PEFRILO’). Prior to giving PEFRILO, you should inform their health care provider about all other medications that your child is taking. While giving PEFRILO, your child should not start any new medications without informing the health care provider.
If you are taking an oral contraceptive or using a patch contraceptive to prevent pregnancy, you should use an additional or different type of contraception (e.g. barrier contraceptives such as condoms) since PEFRILO may reduce the effectiveness of oral and patch contraceptives.

PEFRILO may interact with medicines used for erectile dysfunction (e.g. sildenafil, tadalafil, vardenafil). You should never take vardenafil with PEFRILO. If you are

taking sildenafil or tadalafil with PEFRILO, you should talk to your health care provider about possible interactions with other medicines and side effects.

Tell the health care provider if your child is taking corticosteroids such as dexamethasone, prednisolone or fluticasone. This includes use of nasal or oral inhalators against rhinitis and asthma. PEFRILO may raise the blood levels of these medicines and cause serious side effect (Cushing's syndrome with hypertension, diabetes, a rounded face, loss of fat on arms and legs as well as a reduction in the body's production of the hormone cortisol). The health care provider may wish to reduce the steroid dose or monitor the side effects more closely.

Other medicines and PEFRILO

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

It is important that you tell your child's health care provider if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of PEFRILO or PEFRILO may affect their action (see also above, sections 'do not take PEFRILO' and "Warnings and precautions"). Side effects of either medicine may become worse or the medicines may become less effective. Sometimes your health care provider may adjust the dose of PEFRILO or of the other medicine. Examples of medicines that are or may be unsuitable to take with PEFRILO or where dose adjustments may be necessary, include:

- Amprenavir, efavirenz, fosamprenavir, indinavir, maraviroc, nelfinavir, nevirapine, saquinavir, tipranavir (against HIV) antiviral medicine used to treat

chronic hepatitis C virus (HCV) infection in adults (e.g. boceprevir, simeprevir and telaprevir);

- Rifampicin, rifabutin, bedaquiline, delamanid (against tuberculosis);
- Clarithromycin (antibiotic);
- Voriconazole, itraconazole, ketoconazole (against fungal infections);
- Methadone, fentanyl, propoxyphene, pethidine (opioid analgesics, to treat severe pain);
- Medicines to treat asthma and other lung-related problems such as chronic obstructive pulmonary disease (COPD) (e.g. salmeterol);
- Ifosfamide, vincristine, vinblastine, etoposide, dasatinib and nilotinib (to treat cancer);
- Warfarin, rivaroxaban, vorapaxar (to prevent blood clots);
- Carbamazepine, phenytoin, lamotrigine, phenobarbital, valproate (to treat seizures);
- Trazodone, bupropion (against depression);
- Anti-gout medicine (colchicine);
- Medicine used to treat chronic hepatitis C in adults (e.g. boceprevir, simeprevir and telaprevir);
- Erectile dysfunction medicines (e.g. sildenafil and tadalafil);
- Digoxin, (to treat heart conditions);
- Diltiazem, amlodipine, felodipine, nifedipine, nicardipine (calcium channel blockers, to treat high blood pressure);
- Bepridil, systemic lidocain, quinidine (used to correct heart rhythm);
- Maracivoc (HIV CCR5-antagonist);
- Raltegravir (HIV-1 integrase inhibitor);
- Simvastatin, atorvastatin, rosuvastatin, lovastatin (to lower blood cholesterol);

- Ciclosporin, sirolimus (rapamycin), tacrolimus (to reduce the body's immune response, e.g. after organ transplantation);
- Medicines to treat pulmonary arterial hypertension (high blood pressure in the pulmonary artery) (e.g. bosentan, sildenafil, tadalafil);
- Sedative, used to treat anxiety and to help you sleep (e.g. midazolam by injection);
- Fusidic acid used to treat long-term infections of the bones and joints (e.g. osteomyelitis);
- Medicines used for smoking cessation (e.g. bupropion);
- Oral contraceptive or using a patch contraceptive to prevent pregnancy ;
- Steroids (e.g. budesonide, dexamethasone, fluticasone propionate, ethinyl oestradiol.

PEFRILO with food and drink

PEFRILO must be taken with food.

Pregnancy, breast-feeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking PEFRILO.

Pregnant or breast-feeding women should not take PEFRILO. The healthcare provider should be told immediately if you are pregnant or think you are pregnant. If a mother wants to breast-feed her baby, her health care provider should be asked for advice on the risks and benefits. Treatment of mother or child or both with medicines may be needed.

Generally it is recommended that HIV-infected women should not breast-feed their

infants because of the possibility that the baby may be infected with HIV through the breast milk.

Driving and using machines

PEFRILO may cause side effects such as drowsiness or headache, that can reduce the ability to drive and to use machines.

PEFRILO contains mannitol

PEFRILO contains mannitol and may have a laxative effect.

3. How to give PEFRILO

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

Always take PEFRILO exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The recommended doses of PEFRILO in infants is as follows:

Child's weight	Dose (twice daily)
6 – 9,9 kg	3 sachets in the morning 3 sachets in the evening
10 – 13.9 kg	4 sachets in the morning 4 sachets in the evening
14 – 19,9 kg	5 sachets in the morning 5 sachets in the evening
20 – 24,9 kg	6 sachets in the morning 6 sachets in the evening

Your child's health care provider may adjust the dose in case your child is receiving certain other medicines.

Your child should receive each dose of PEFRILO about 12 hours apart.

PEFRILO must be taken with a meal twice daily. PEFRILO should be sprinkled/mixed with soft food such as applesauce or porridge, or mixed with liquid such as water, as described below. PEFRILO should not be chewed or crushed.

For infants and young children older than 6 months of age who are able to take soft foods:

1. Determine the number of sachets needed to prepare a dose.
2. Prior to mixing, tap the sachet(s) to move all the granules to the bottom of the sachet(s).
3. Completely tear or cut off the top of the sachet(s) and make sure the sachet(s) are fully open.
4. Mixing with soft food such as applesauce or porridge: Using a spoon, mix the entire contents of the PEFRILO sachet(s) with soft food (approximately 1 teaspoon of soft food for 1 sachet; 2 teaspoons for 2 sachets, etc.) in a small cup or bowl. Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the small cup/bowl or spoon, add more soft food to the granules and mix. Then give or take the mixture along with adequate drinking water, to ensure that no granules are left behind in the mouth.
5. Mixing with liquid such as drinking water: Mix the entire contents of the PEFRILO sachet(s) with approximately 5 - 15 ml of drinking water (1 teaspoon of water for 2 sachets; 2 teaspoons of water for 3 to 8 sachets; 3 teaspoons or 1 tablespoon for 10 sachets). Make sure no granules/powder are left inside the sachet(s). Give or take all of the mixture. If any granules are left in the spoon, add more liquid (water) and mix. Then give or take the mixture.

6. Administer the medicine/food mixture within 2 hours of preparation. If not administered within 2 hours of preparation, throw away the mixture and prepare a new dose.
7. No mixture of the granules and food is to be stored for later use.
8. Repeat above steps for next dose.

If your child takes more PEFRILO than he/she should

If your child has taken too many granules or if someone accidentally swallows some, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you forget to give your child PEFRILO

If your child accidentally misses a dose and you notice within 6 hours have the child take the missed dose as soon as possible. The next normal dose should be taken at the regular time as prescribed by your health care provider.
If you notice later, then simply have the child take his/her normal dose when the next one is due. Do not give a double dose to make up for forgotten individual doses.

Effects when treatment with PEFRILO is stopped:

Because the medicine controls and does not cure the condition, your child will normally need to take it continuously. The treatment should not be stopped unless your child's health care provider tells you so.

4. Possible side effects

PEFRILO can have side effects.

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

If any of the following happens, stop taking PEFRILO 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,
- rash or itching.

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

Frequency not known

- yellowing of the skin or whites of eye (jaundice),
- severe or life-threatening skin rashes and blisters (Stevens-Johnson syndrome and erythema multiforme).

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:

- diarrhoea,

- nausea,
- upper respiratory tract infection,
- changes in body shape or face shape due to changes in fat distribution,
- headache including migraine,
- difficulty in sleeping,
- dizziness, anxiety,
- feeling, tired, lack of strength and energy,
- vomiting, enlarged abdomen, abdominal pain, passing wind, indigestion, decreased appetite, reflux from your stomach to your oesophagus which may cause pain,
- swelling or inflammation of the stomach, intestines and colon,
- increased cholesterol, increased triglycerides,
- high blood pressure,
- inflammation of the pancreas,
- decreased ability of the body to handle sugar including diabetes mellitus, weight loss,
- low number of red blood cells, low number of white blood cells which are usually used to fight infection,
- inflammation of the liver including increased liver enzymes,
- muscle disorders such as weakness and spasms, pain in the joints, muscles and back,
- night sweats,
- rash, eczema, accumulation of scales or greasy skin,
- itching, rash including raised bumps on the skin, infection of the skin, inflammation of skin or hair pores, accumulation of fluid in cells or tissues,
- allergic reactions including hives and inflammation in the mouth,

- tingling, prickling or numbness of the skin,
- haemorrhoids,
- lower respiratory tract infection,
- enlargement of the lymph nodes,
- impotence, abnormally heavy or extended menstrual flow or a lack of menstruation.

Further information about nausea, vomiting or abdominal pain

Tell your health care provider if you have nausea, vomiting or abdominal pain as these may be suggestive of pancreatitis (inflammation of the pancreas).

Further information about increased cholesterol and triglycerides

The long-term risks for complications such as heart attacks or stroke due to increased triglycerides and cholesterol are not known at this time.

Your health care provider will monitor you, and may prescribe other medicines if needed. Large increases in the amount of triglycerides (fats in the blood) have been considered a risk factor for pancreatitis. Tell your health care provider if you notice any changes in your body shape due to changes in fat distribution.

Less frequent side effects:

- loss or changed sense of taste,
- hearing a sound such as buzzing, ringing or whistling,
- abnormal vision, eye disorder,
- atrioventricular block—an abnormality in your electrocardiogram,
- plaque building up inside your arteries which could lead to heart attack and stroke,
- inflammation of blood vessels and capillaries,

- inflammation of the bile duct,
- uncontrolled shaking of the body,
- constipation,
- dry mouth,
- inability to control your bowels,
- inflammation of the first section of the small intestine just after the stomach, wound or ulcer in the digestive tract, bleeding from the intestinal tract or rectum,
- red blood cells in the urine,
- fatty deposits in the liver, enlarged liver,
- lack of functioning of the testes,
- a flare-up of symptoms related to an inactive infection in your body (immune reconstitution),
- increased appetite,
- abnormally high level of bilirubin (a pigment produced from the breakdown of red blood cells) in the blood,
- decreased sexual desire,
- inflammation of the kidney,
- bone death caused by poor blood supply to the area,
- mouth sores or ulcerations, inflammation of the stomach and intestine,
- kidney failure,
- breakdown of muscle fibres resulting in the release of muscle fibre contents (myoglobin) into the bloodstream,
- tremor,
- abnormal closure of one of the heart valves (tricuspid valve),
- vertigo (spinning feeling),

- weight gain,
- abnormal dreams,
- hair loss,
- deep vein inflammation related to a blood clot.

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. 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://sahpra.org.za/wpcontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf
By reporting side effects, you can help provide more information on the safety of PEFRILO.

5. How to store PEFRILO

Store all medicines out of reach of children.

- Store at or below 30 °C in the original container.
- 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 PEFRILO contains

The active substances are lopinavir and ritonavir.

Each sachet contains 40 mg lopinavir and 10 mg ritonavir.

Each sachet contains 583 mg of mannitol.

The other ingredients are:

Acesulfame potassium, copovidone, colloidal silicon dioxide, ethyl cellulose, mannitol, sodium stearyl fumarate, sorbitan monolaurate and vanilla flavour.

What PEFRILO looks like and contents of the pack

PEFRILO contains white to creamish granular powder filled in a sachet.

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Contents of the pack:

Sachets, comprises of printed triple laminated roll with aluminium foil, soft, dull side PET and bright side laminated to PE film. 1,000 mg granules per sachet.

Pack size: 120 sachets per carton.

Holder of Certificate of Registration

VIATRIS HEALTHCARE (PTY) LTD

4 Brewery street

Isando

Gauteng

Republic of South Africa

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Access to the corresponding Professional Information

To be confirmed.