

WHO-PQ RECOMMENDED PATIENT INFORMATION LEAFLET

*This patient information leaflet focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.**

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

* https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf

Information for the patient

[HA697 trade name][†]
lopinavir/ritonavir

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 questions about the medicine, ask your health care provider.
- This medicine has been prescribed for your child only. Do not pass it on to others. It may harm them, even if their signs of illness seem to be the same as your child's.
- If you are concerned about any side effects, talk to your health care provider. This includes unwanted effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [HA697 trade name] is and what it is used for
2. What you need to know before you give [HA697 trade name] to your child
3. How to give [HA697 trade name]
4. Possible side effects
5. How to store [HA697 trade name]
6. Contents of the pack and other information

1. What [HA697 trade name] is and what it is used for

[HA697 trade name] is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in infants and children patients 14 days and older weighing over 3 kg. It slows down the spread of infection in your child's body. [HA697 trade name] is an antiretroviral medicine. It belongs to a group of medicines called protease inhibitors.

[HA697 trade name] 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 product is intended for use in children. Safety information on use in adults is also provided

2. What you need to know before you give [HA697 trade name] to your child

Do not give your child [HA697 trade name]:

- if your child is allergic (hypersensitive) to lopinavir, ritonavir, or any of the other ingredients of [HA697 trade name] listed in section 6.
- 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])

[†]Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

- 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 Taking Other Medicines).
- 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 ‘Taking other medicines’ 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

Check with your health care provider before giving [HA697 trade name] to your child if your child :

- * has had liver disease—patients with chronic hepatitis B or C treated with antiretroviral agents such as [HA697 trade name] 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)—[HA697 trade name] may increase the risk of bleeding.
- * has diabetes—treatment with HIV protease inhibitors like [HA697 trade name] 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 [HA697 trade name] 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 [HA697 trade name]) 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 [HA697 trade name] may affect the heart rhythm. If your child has or has had any heart problems, you should tell the health care provider before giving [HA697 trade name].

[HA697 trade name] may interact with other medications, which may alter their effects (see also the section above, 'do not take [HA697 trade name]', and below 'taking other medicines'). Prior to giving [HA697 trade name], you should inform their health care provider about all other medications that your child is taking. While giving [HA697 trade name], your child should not start any new medications without informing the health care provider.

If one is 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 [HA697 trade name] may reduce the effectiveness of oral and patch contraceptives.

[HA697 trade name] may interact with medicines used for erectile dysfunction (e.g. sildenafil, tadalafil, vardenafil). You should never take vardenafil with [HA697 trade name]. If you are taking sildenafil or tadalafil with [HA697 trade name], 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. [HA697 trade name] may raise the blood levels of these drugs 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.

Taking other 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

[HA697 trade name] or [HA697 trade name] may affect their action (see also above, sections ‘do not take [HA697 trade name]’ 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 [HA697 trade name] or of the other drug. Examples of drugs that are or may be unsuitable to take with [HA697 trade name] 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.

Taking [HA697 trade name] with food and drink

[HA697 trade name] may be taken with or without food.

Pregnancy and breast-feeding

Pregnant or breast-feeding women should not take [HA697 trade name] unless specifically directed by the health care provider. 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

[HA697 trade name] may cause side effects such as drowsiness or headache, that can reduce the ability to drive and to use machines.

Other ingredients of [HA697 trade name]

[HA697 trade name] contains mannitol, which may have a mild laxative effect.

3. How to give [HA697 trade name]

[HA697 trade name] should always be given exactly as described by the health care provider. You should check with the health care provider if you are not sure.

The recommended doses of [HA697 trade name] in infants and children weighing over 3 kg is as follows:

Child's weight	Dose (twice daily)
3–5.9 kg	2 sachets in the morning 2 sachets in the evening
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 [HA697 trade name] about 12 hours apart.

How to give [HA697 trade name]

[HA697 trade name] must be taken with a meal twice daily. [HA697 trade name] should be sprinkled/mixed with soft food such as applesauce or porridge, or mixed with liquid such as water, as described below.

[HA697 trade name] 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 Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg 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 Lopinavir / Ritonavir Oral Granules 40 mg / 10 mg 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 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 drug/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.

For infants not yet taking solid food, i.e. less than 6 months of age:

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. Granules can be added to a small volume of expressed breast milk or formula in a spoon and given to the infant or put directly on the infant's tongue before breast-feeding.
5. Give the entire dose of granules to the infant immediately.
6. It is important to make sure the infant has taken the entire dose of granules by limiting the breast milk (or formula) used to an amount the infant is able to easily consume in few swallows (e.g. two or three teaspoons), which may be followed by additional breast milk (or formula) to ensure the full dose is ingested.
7. Repeat above steps for next dose.

If your child takes more [HA697 trade name] than he/she should

If your child has taken too much granules or if someone accidentally swallows some, you should contact your child's health care provider or the nearest hospital emergency department for further advice.

If you forget to give your child [HA697 trade name]

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.

If your child stops taking [HA697 trade name]

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

Like all medicines, [HA697 trade name] can cause side effects, but not everybody gets them. When treating HIV infection, it is not always possible to tell which unwanted effects are caused by [HA697 trade name] and which are caused by any other medicines you may be taking at the same time, and by the HIV disease.

Tell your health care provider of any change in your health.

Very common side effects (affects more than 1 person in every 10 who take this medicine):

- * Diarrhoea
- * Nausea
- * Upper respiratory tract infection

Common side effects (affects between 1 and 10 person in every 100 who take this medicine):

- * 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.

Uncommon side effects (affects 1 to 10 users in 1,000):

- * 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

Other side effects reported with [HA697 trade name]: yellowing of the skin or whites of eye (jaundice), severe or life-threatening skin rashes and blisters (Stevens-Johnson syndrome and erythema multiforme). It is not known how frequently these effects occur.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your health care provider.

Reporting of side effects

If your child gets any side effects, talk to your health care provider. This includes unwanted effects not listed in this leaflet. If available, you can also report side effects directly through the national reporting system. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [HA697 trade name]

Keep this medicine out of the sight and reach of children.

Do not store above 30°C. Store in the original container.

Do not use this medicine after the expiry date stated on the sachet label and carton, after “EXP”. The expiry date refers to the last day of that month.

Do not use this medicine if you notice description of the visible signs of deterioration that it is different from the description below.

Do not throw away any medicines in wastewater or household waste. Ask your health care provider how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [HA697 trade name] contains

- The active ingredients are lopinavir 40 mg and ritonavir 10 mg.
- The other ingredients of [HA697 trade name] are copovidone, sorbitan monolaurate, colloidal silicon dioxide, ethyl cellulose, mannitol, acesulfame potassium, sodium stearyl fumarate and vanilla flavour.

What [HA697 trade name] looks like and contents of the pack

A white to creamish granular powder filled in a sachet.

Pack size: 120 sachets per carton

Supplier and Manufacturer

Supplier

Mylan Laboratories Limited
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad-500096
Telangana
India
Email: Imtiyaz.Basade@viatris.com

Manufacturer

Mylan Laboratories Limited
F4 & F12, MIDC, Malegaon
Sinnar, Nashik – 422 113
Maharashtra
India

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Detailed information on this medicine is available on the World Health Organization (WHO) website:
<https://extranet.who.int/pqweb/medicines>