

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 (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.*

Information for the patient

[HA650 trade name]¹

Lopinavir / Ritonavir 100 mg/25 mg Tablets

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 you only. Do not pass it on to others. It may harm them, even if their signs of illness seem to be the same as yours.
- If you get 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 [HA650 trade name] is and what it is used for
2. What you need to know before you take [HA650 trade name]
3. How to take [HA650 trade name]
4. Possible side effects
5. How to store [HA650 trade name]
6. Contents of the pack and other information

1. What [HA650 trade name] is and what it is used for

[HA650 trade name] is used for the treatment of human immunodeficiency virus (HIV) infection in adults and children weighing 10 kg or more. It slows down the spread of infection in the body. [HA650 trade name] is an antiretroviral medicine. It belongs to a group of medicines called protease inhibitors.

[HA650 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 you.

2. What you need to know before you take [HA650 trade name]

Do not take [HA650 trade name]:

- if you are allergic (hypersensitive) to lopinavir, ritonavir, or any of the other ingredients of [HA650 trade name] listed in section 6.
- if you have severe liver problems
- If you are 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)

¹Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

- Alfuzosin (used in men to treat symptoms of an enlarged prostate [benign prostatic hyperplasia])
- 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 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 doctor'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 you are taking any of these medicines, ask your healthcare provider about making changes either in the treatment for your other condition(s) or in your antiretroviral treatment.

Warnings and precautions

Check with your healthcare provider before taking [HA650 trade name] if you or your child:

- * have had liver disease—patients with chronic hepatitis B or C treated with antiretroviral agents such as [HA650 trade name] are at an increased risk for severe and potentially fatal liver adverse reactions, and may require blood tests to monitor liver function.
- * have haemophilia type A and B (a disorder of blood coagulation)—[HA650 trade name] may increase the risk of bleeding.
- * have diabetes—treatment with HIV protease inhibitors like [HA650 trade name] may occasionally cause or aggravate diabetes.

This medicine helps to control HIV infection, but it is not a cure for it. You 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 the medicine without first talking to your health care provider.

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

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

Tell your health care provider if your blood cholesterol is high. Treatment with [HA650 trade name] may increase blood cholesterol and other blood lipids. Therefore, you may require blood tests during treatment.

In rare cases, patients receiving lopinavir and ritonavir (contained in [HA650 trade name]) have developed pancreatitis (inflammation of the pancreas). You should contact the health care provider if you get 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 your health care provider immediately.

In addition to opportunistic infections, autoimmune disorders (resulting from the immune system attacking healthy body tissue) may also occur after you start 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, tell your 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 [HA650 trade name] may affect the heart rhythm. If have or have had any heart problems, you should tell your healthcare provider before taking [HA650 trade name].

[HA650 trade name] may interact with other medications, which may alter their effects (see also the section above, 'do not take [HA650 trade name]', and below 'taking other medicines'). Prior to taking [HA650 trade name], you should inform your health care provider about all other medications that you are taking. While taking [HA650 trade name], you should not start any new medications without informing your 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 [HA650 trade name] may reduce the effectiveness of oral and patch contraceptives.

[HA650 trade name] may interact with medicines used for erectile dysfunction (e.g. sildenafil, tadalafil, vardenafil). You should never take vardenafil with [HA650 trade name]. If you are taking sildenafil or tadalafil with [HA650 trade name], you should talk to your health care provider about possible interactions with other medicines and side effects.

Tell your health care provider if you are taking corticosteroids such as dexamethasone, prednisolone or fluticasone. This includes use of nasal or oral inhalators against rhinitis and asthma. [HA650 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). Your 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 health care provider if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of [HA650 trade name] or [HA650 trade name] may affect their action (see also above, sections 'do not take [HA650 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 [HA650 trade name] or of the other drug. Examples of drugs that are or may be unsuitable to take with [HA650 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 [HA650 trade name] with food and drink

[HA650 trade name] may be taken with or without food.

Pregnancy and breast-feeding

Pregnant or breast-feeding women should not take [HA650 trade name] unless specifically directed by the health care provider. The health-care provider should be told immediately if you are pregnant or think you are pregnant.

If a mother wants to breastfeed her baby, her healthcare provider should be asked for advice on the risks and benefits. Treatment of mother and/or child 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

[HA650 trade name] may cause side effects such as drowsiness or headache, that can reduce the ability to drive and to use machines.

3. How to take [HA650 trade name]

[HA650 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 dosage of [HA650 trade name] in adult patients and adolescents weighing 35 kg or more is four tablets twice daily, taken with or without food.

The recommended dosage of [HA650 trade name] in patients weighing at least 25 kg but less than 35 kg is three tablets twice daily, taken with or without food.

The recommended dosage of [HA650 trade name] for patients weighing at least 14 kg but less than 25 kg is two tablets twice daily taken with or without food.

The recommended dosage of [HA650 trade name] for patients weighing at least 10 kg but less than 14 kg is two tablets in the morning and one tablet in the evening taken with or without food.

The health care provider may adjust the dose in case of co-treatment e.g. with certain other anti-HIV drugs.

For patients weighing 35 kg or more, formulations containing 200/50 mg lopinavir/ritonavir should preferably be used, if available, to reduce the daily tablet count.

For patients weighing less than 10 kg other formulations with lower amounts of the active substances are available.

Take each dose of [HA650 trade name] approximately 12 hours apart.

[HA650 trade name] should be swallowed whole and not chewed, broken or crushed.

Swallow [HA650 trade name] with water or another drink.

4. Possible side effects

Like all medicines, [HA650 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 [HA650 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 [HA650 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.

If you take more [HA650 trade name] than you should

If you take too many tablets of [HA650 trade name], contact your health care provider for advice.

If possible, show them the [HA650 trade name] pack.

If you forget to take [HA650 trade name]

If you miss a dose of [HA650 trade name], take it as soon as you remember. But if your next dose is due within 6 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before.

You must not take a double dose to make up for a missed dose.

If you stop taking [HA650 trade name]

Do not stop or change the daily dose of [HA650 trade name] without first checking with your health care provider.

You should take [HA650 trade name] every day as recommended to help control your HIV infection, no matter how much better you feel. Using [HA650 trade name] as recommended gives the best chance of delaying the development of resistance to the product.

If a side effect stops you from taking [HA650 trade name] tell your health care provider right away.

Always make sure you have enough [HA650 trade name] so you don't run out

Reporting of side effects

If you get 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 [HA650 trade name]

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

Do not use this medicine after the expiry date stated on the bottle label after EXP. The expiry date refers to the last day of that month.

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 [HA650 trade name] contains

- The active substances are lopinavir 100mg and ritonavir 25mg
- The other ingredients of [HA650 trade name] are excipients:
Core tablet: Copovidone, sorbitan monolaurate, colloidal silicon dioxide, sodium stearate fumarate
Film coating: Hypromellose, Hydroxypropyl cellulose, titanium dioxide, colloidal anhydrous silica, polysorbate, macrogol, talc, iron oxide yellow

What [HA650 trade name] looks like and contents of the pack

Yellow, capsule-shaped, biconvex film coated tablets, debossed with 'H' on one side and 'L7' on the other side. No score-line.

The tablet should not be divided.

120 tablets are supplied in 150cc high density polyethylene (HDPE) bottles closed with 38mm child-resistant polypropylene plastic caps with pulp liners.

Supplier

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For any information about this medicine, contact the local representative of the supplier.

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Detailed information on this medicine is available on the World Health Organization (WHO) web site:
<https://extranet.who.int/prequal/>.