

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/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

Information for the patient

[HA565 trade name][†]
Ritonavir Tablets USP

*The warnings and instructions in this leaflet are intended for the person taking the medicine.
If you are a parent or carer responsible for giving the medicine to someone else such as a child,
you will need to apply the instructions accordingly.*

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 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 [HA565 trade name] is and what it is used for
2. What you need to know before you take [HA565 trade name]
3. How to take [HA565 trade name]
4. Possible side effects
5. How to store [HA565 trade name]
6. Contents of the pack and other information

1. What [HA565 trade name] is and what it is used for

[HA565 trade name] is an antiretroviral medicine used in the treatment of HIV-1 infected patients.

[HA565 trade name] is taken in combination with protease inhibitors and acts as a booster (pharmacokinetic enhancer) to help improve their effect. It does this by slowing down the breakdown of the protease inhibitors which will make them stay in the body for longer.

Your health care provider will discuss with you the best combination of medicines for you.

[HA565 trade name] contains the active substance ritonavir.

To control your HIV infection, and to stop your illness from getting worse, you must take all your HIV medicines regularly, unless your health care provider tells you to stop taking any.

2. What you need to know before you take [HA565 trade name]

Do not take [HA565 trade name]

- if you are **allergic** to ritonavir, or any of the other ingredients of this medicine (listed in section 6).
- if you have **severe liver disease**.
- if you are currently taking any of the following medicines:

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

<i>Astemizole or terfenadine</i>	to treat allergy symptoms – these medicines may be available without prescription
<i>Amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine</i>	to correct irregular heartbeats
<i>Ergotamine, dihydroergotamine</i>	to treat migraine and headaches
<i>Ergometrine and methylergonovine</i>	to stop excessive bleeding that may occur following childbirth or an abortion
<i>Clorazepate, diazepam, estazolam, flurazepam, triazolam or oral (taken by mouth) midazolam</i>	to help you sleep and/or relieve anxiety
<i>Lurasidone, clozapine, pimozide, or quetiapine</i>	to treat psychiatric conditions
<i>Ranolazine</i>	to treat chronic chest pain [angina]
<i>Pethidine, piroxicam, propoxyphene</i>	to relieve pain
<i>Cisapride</i>	to treat some stomach conditions
<i>Lovastatin and simvastatin, and lomitapide</i>	to lower cholesterol levels
<i>Neratinib</i>	to treat breast cancer
<i>Alfuzosin</i>	to treat enlarged prostate
<i>Fusidic acid</i>	to treat bacterial infections
<i>Sildenafil</i>	to treat high blood pressure in the lungs if you suffer from a lung disease called pulmonary arterial hypertension that makes breathing difficult. Patients without this disease may use sildenafil for impotence (erectile dysfunction) under their doctor's supervision (see the section on Other medicines and [HA565 trade name])
<i>Avanafil or vardenafil</i>	to treat erectile dysfunction
<i>Colchicine</i>	to treat gout or familial Mediterranean fever. If you have kidney and/or liver problems; see the section on Other medicines and [HA565 trade name].
products that contain <i>St John's wort</i> (<i>Hypericum perforatum</i>)	often used in herbal medicines that you can buy without prescription.

If you are currently taking any of these medicines, ask your health care provider about switching to a different medicine while you are taking [HA565 trade name]. Also read the list of medicines under '**Other medicines and [HA565 trade name]**' for use with certain other medicines which require special care.

Warnings and precautions

Talk to your health care provider before taking [HA565 trade name].

Important information

- It is important that you also carefully read the leaflets that are provided with the other medicines you are taking with [HA565 trade name]. There may be additional information in those leaflets about situations when ritonavir should be avoided. If you have any further questions about this medicine or the other medicines prescribed, please ask your doctor or pharmacist.

- People taking ritonavir in combination with other HIV medicines may still develop infections or other illnesses associated with HIV infection or AIDS. It is therefore important that you remain under the supervision of your health care provider while taking this medicine.
- 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.

Tell your healthcare provider if you have/had:

- A history of **liver disease**.
- **Hepatitis B or C**, and are being treated with a combination of antiretroviral agents, as you are at a greater risk of a severe and potentially life threatening reaction because of the effect on the liver. Regular blood tests may be required to check your liver is working properly.
- **Haemophilia**, as there have been reports of increased bleeding in patients with haemophilia who are taking this type of medicine (protease inhibitors). The reason for this is not known. You may need to take additional medicines to help your blood clot (factor VIII), in order to control any bleeding.
- **Erectile dysfunction**, as the medicines used to treat erectile dysfunction can cause low blood pressure (hypotension) and prolonged erection.
- **Diabetes**, as there have been reports of worsening of or the development of diabetes (diabetes mellitus) in some patients taking protease inhibitors.
- **Kidney (renal) disease**, since your healthcare provider may need to check the dose of your other medicines (such as protease inhibitors).

Tell your healthcare provider if you experience:

- **Diarrhoea** or **vomiting** that is not improving (persistent), as this may reduce how well the medicines you are taking work.
- **Feeling sick** (nausea), **vomiting** or have **stomach pain**, because these may be signs of inflammation of the pancreas (pancreatitis). Some patients taking ritonavir can develop serious problems with their pancreas. Tell your healthcare provider as soon as possible if this applies to you.
- **Symptoms of infection** – inform your healthcare provider immediately. Some patients with advanced HIV infection (AIDS) who then start anti-HIV treatment may develop the symptoms of infections they have had in the past even if they didn't know they had had them. It is believed that this happens because the body's immune response improves and helps the body to fight these infections. In addition to these opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking 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 healthcare provider immediately to seek necessary treatment.
- **Joint stiffness, aches and pains** (especially of the hip, knee and shoulder) and difficulty moving, as this may be a sign of a problem that can destroy bone (osteonecrosis). Some patients taking a number of antiretroviral medicines may develop this disease.
- **Muscle pain, tenderness or weakness**, particularly in combination with antiretroviral therapy including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious (See section 4, Possible side effects).
- **Dizziness, lightheadedness, fainting spells or abnormal heartbeat**. Some patients taking ritonavir may experience changes in the electrocardiogram (ECG). Tell your healthcare provider if you have a heart defect or conduction defect.
- If you have any other health concerns, discuss these with your healthcare provider as soon as you can.

Other medicines and [HA565 trade name]

Tell your health care provider if you are taking or have recently taken or might take any other medicines, including medicines without a prescription.

There are some medicines that you cannot take at all with [HA565 trade name]. These are mentioned above under 'Do not take [HA565 trade name]'.

The following warnings apply when ritonavir is taken at higher doses. However, these warnings may also apply when it is used in lower doses (a booster) with other medicines. Tell your health care provider if you are taking any of the medicines listed below, as special care should be taken.

- **Sildenafil or tadalafil** for impotence (erectile dysfunction). The dose and/or frequency of use of these medicines may need to be reduced to avoid low blood pressure (hypotension) and prolonged erection. You must not take ritonavir with sildenafil if you suffer from pulmonary arterial hypertension (see also '**Do not take [HA565 trade name]**' above). Tell your health care provider if you are taking tadalafil for pulmonary arterial hypertension.
- **Colchicine** (for gout) as ritonavir may raise the blood levels of this medicine. You must not take ritonavir with colchicine if you have kidney and/or liver problems (see also '**Do not take [HA565 trade name]**' above).
- **Digoxin** (heart medicine). Your health care provider may need to adjust the dose of digoxin and monitor you while you are taking digoxin and [HA565 trade name] in order to avoid heart problems.
- **Hormonal contraceptives** containing ethinyl oestradiol as ritonavir may reduce the effectiveness of these medicines. It is recommended that a condom or other non-hormonal method of contraception is used instead. You may also notice irregular uterine bleeding if you are taking this type of hormonal contraceptive with ritonavir.
- **Atorvastatin or rosuvastatin** (for high cholesterol) as ritonavir may raise the blood levels of these medicines. Talk to your health care provider before you take any cholesterol-reducing medicines with [HA565 trade name] (see also '**Do not take [HA565 trade name]**' above).
- **Steroids** (e.g. dexamethasone, fluticasone propionate, prednisolone, triamcinolone) as ritonavir may raise the blood levels of these medicines which may lead to Cushing's syndrome (development of a rounded face) and reduce production of the hormone cortisol. Your health care provider may wish to reduce the steroid dose or monitor your side effects more closely.
- **Trazodone** (a medicine for depression) as unwanted effects like nausea, dizziness, low blood pressure and fainting can occur when taken with ritonavir.
- **Rifampicin and saquinavir** (used for tuberculosis and HIV, respectively) as serious liver damage can occur when taken with ritonavir.
- **Bosentan, riociguat** (used for pulmonary arterial hypertension) as ritonavir may increase the blood levels of this medicine.

There are medicines that may not be mixed with [HA565 trade name] because their effects could increase or decrease when taken together. In some cases your doctor may need to perform certain tests, change the dose or monitor you regularly. This is why you should tell your health care provider if you are taking any medicines, including those you have bought yourself or herbal products, but it is especially important to mention these:

- amphetamine or amphetamine derivatives;
- antibiotics (e.g. erythromycin, clarithromycin);
- anticancer treatments (e.g. abemaciclib; afatinib, apalutamide, ceritinib, encorafenib, dasatinib, ibrutinib, nilotinib, venetoclax, vincristine, vinblastine);
- medicines used to treat low blood platelet count (e.g. fostamatinib);
- anticoagulants (e.g. rivaroxaban, vorapaxar, warfarin);
- antidepressants (e.g. amitriptyline, desipramine, fluoxetine, imipramine, nefazodone, nortriptyline, paroxetine, sertraline, trazodone);
- antifungals (e.g. ketoconazole, itraconazole);
- antihistamines (e.g. loratidine, fexofenadine);
- antiretroviral medicines including HIV-protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir) non-nucleoside reverse transcriptase

- inhibitors (NNRTI) (delavirdine, efavirenz, nevirapine), and others (didanosine, maraviroc, raltegravir, zidovudine);
- anti-tuberculosis medicine (bedaquiline and delamanid);
 - antiviral medicine used to treat chronic hepatitis C virus (HCV) infection in adults (e.g. glecaprevir/pibrentasvir and simeprevir);
 - anxiety medicine, buspirone;
 - asthma medicine, theophylline, salmeterol;
 - atovaquone, a medicine used to treat a certain type of pneumonia and malaria;
 - buprenorphine, a medicine used for the treatment of chronic pain;
 - bupropion, a medicine used to help you stop smoking;
 - epilepsy medicines (e.g. carbamazepine, divalproex, lamotrigine, phenytoin);
 - heart medicines (e.g. disopyramide, mexiletine and calcium channel antagonists such as amlodipine, diltiazem and nifedipine);
 - immune system suppressant (e.g. cyclosporine, tacrolimus, everolimus);
 - levothyroxine (used to treat thyroid problems);
 - morphine and morphine-like medicines used to treat severe pain (e.g. methadone, fentanyl);
 - sleeping pills (e.g. alprazolam, zolpidem) and also midazolam administered by injection;
 - tranquillisers (e.g. haloperidol, risperidone, thioridazine);
 - colchicine, a treatment for gout.

[HA565 trade name] with food and drink

[HA565 trade name] tablets should be taken with food.

Pregnancy and breast-feeding

Pregnancy

If you become pregnant, or are planning to become pregnant, you must contact your health care provider to discuss the potential adverse effects and the benefits and risks of your antiretroviral therapy to you and your child.

Breastfeeding

If you are interested in breastfeeding your baby, you should discuss the risks and benefits with your health care provider.

Driving and using machines

Do not operate machines or drive if you feel dizzy after taking [HA565 trade name].

3. How to take [HA565 trade name]

Always take [HA565 trade name] exactly as your health care provider has told you. You should check with your health care provider if you are not sure.

It is important that the tablets are swallowed whole and not chewed, broken or crushed.

The recommended dose is usually 1 or 2 tablets per day depending on the other protease inhibitor this medicine is taken with.

This medicine should be taken with food. For more detailed dose recommendations, see the Patient Information Leaflets of the other anti-HIV medicines that are being taken.

This medicine should only be taken by people who can swallow tablets whole. Other, more suitable formulations may be available for children weighing less than 25 kg or people not able to swallow tablets whole.

You should take [HA565 trade name] with other HIV medicines every day to help control your HIV, no matter how much better you feel. If a side effect is preventing you from taking the tablets as directed, tell your health care provider straight away. During episodes of diarrhoea your health care provider may decide that extra monitoring is needed.

Always keep enough of this medicine on hand so you don't run out. When you travel or when you need to stay in the hospital, make sure you have enough [HA565 trade name] to last until you can get a new supply.

If you take more [HA565 trade name] than you should

Numbness, tingling, or a “pins and needles” sensation may occur if one takes too much ritonavir. If you realise you have taken more [HA565 trade name] than you were supposed to, contact your health care provider or the Emergency Department of your nearest hospital straight away.

If you forget to take [HA565 trade name]

If you forget to take a dose, take the missed dose as soon as possible. If it is nearly time for the next dose, just take that one. Do not take a double dose to make up for a forgotten dose.

If you stop taking [HA565 trade name]

Even if you feel better, do not stop taking this medicine without talking to your health care provider. Taking [HA565 trade name] as recommended should give you the best chance of delaying resistance to the medicines.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your health care provider will test for these changes.

Like all medicines, [HA565 trade name] can cause side effects, although not everybody gets them. Also, the side effects of [HA565 trade name] when used with other antiretroviral medicines are dependent on the other medicines. It is important that you carefully read the side effects section of the leaflets that are provided with these other medicines.

The frequency of possible side effects listed below is defined using the following convention:

very common	affects more than 1 user in 10
common	affects 1 to 10 users in 100
uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000
not known	frequency cannot be estimated from the available data.

Very common side effects:

- Upper or lower stomach ache
- Vomiting
- Diarrhea (may be severe)
- Feeling sick (nausea)
- Headache
- Flushing, feeling hot
- Dizziness
- Pain in the throat
- Cough
- Upset stomach or indigestion
- A tingling sensation or numbness in the hands, feet or around the lips and mouth
- Feeling weak/tired
- Bad taste in the mouth
- Damage to the nerves that can cause weakness and pain
- Itching
- Rash
- Joint pain and back pain

Common side effects:

- Allergic reactions including skin rashes (may be red, raised, itchy), severe swelling of the skin and other tissues
- Inability to sleep (insomnia)
- Loss of appetite
- Mouth ulcer
- Muscle aches (pain), tenderness or weakness
- Fever

- Anxiety
- Increase in cholesterol
- Increase in triglycerides
- Gout
- Stomach bleeding
- Inflammation of the liver and yellowing of skin or whites of the eyes
- Increase in urination
- Reduced kidney function
- Low level of blood platelets
- Seizures (fits)
- Thirst (dehydration)
- Abnormally heavy periods
- Wind (flatulence)
- Weight loss
- Laboratory test results (such as blood chemistry and blood count)
- Confusion
- Difficulty paying attention
- Fainting
- Blurred vision
- Swelling of the hands and feet
- High blood pressure
- Low blood pressure and feeling faint when getting up
- Coldness in the hands and feet
- Acne

Uncommon side effects:

- Heart attack
- Diabetes
- Kidney failure

Rare side effects:

- Severe or life threatening skin reaction including blisters (Stevens Johnson syndrome, toxic epidermal necrolysis)
- Serious allergic reaction (anaphylaxis)
- High levels of sugar in the blood

Tell your health care provider if you feel sick (nauseous), if you are vomiting, or have stomach pain, because these may be signs of an inflamed pancreas. Also tell your health care provider if you experience joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty moving, as this may be a sign of osteonecrosis. See also section 2, **What you need to know before you take [HA565 trade name]**.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or another protease inhibitor. Should this happen to you, seek immediate advice from your health care provider.

Abnormal liver function tests, hepatitis (inflammation of the liver), and rarely jaundice, have been reported in patients taking [HA565 trade name]. Some people had other illnesses or were taking other medicines. People with liver disease or hepatitis may have worsening of liver disease.

There have been reports of muscle pain, tenderness or weakness, particularly when taking medicines to lower cholesterol in combination with antiretroviral therapy, including protease inhibitors and nucleoside analogues. On rare occasions these muscle disorders have been serious (rhabdomyolysis). In the event of unexplained or continual muscle pain, tenderness, weakness or cramps, stop giving the medicine, contact your health care provider as soon as possible or go to the Emergency Department of your nearest hospital.

Inform your health care provider as soon as possible if you experience any symptoms that suggest an allergic reaction after taking [HA565 trade name] such as rash, hives or breathing difficulties.

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 improve understanding about the safety of this medicine.

5. How to store [HA565 trade name]

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

Do not store above 30°C. Protect from moisture.

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

Do not use this medicine if you notice visible signs of deterioration or 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 [HA565 trade name] contains

- The active ingredient is ritonavir.
- The other ingredients of [HA565 trade name] are:
 - o *Tablet core*: copovidone, colloidal silicon dioxide, sorbitan monolaurate, dibasic calcium phosphate anhydrous and sodium stearyl fumarate
 - o *Film coat*: hypromellose, titanium dioxide, macrogol/PEG, hydroxypropyl cellulose, talc, colloidal anhydrous silica and polysorbate 80

What [HA565 trade name] looks like and contents of the pack

[HA565 trade name] are white to off-white, capsule-shaped, film-coated tablets, debossed with 'H' on one side and 'R9' on the other side.

[HA565 trade name] are available in:

40cc heavy weight high density polyethylene (HDPE) bottles closed with 33mm polypropylene ribbed child-resistant plastic caps with a pulp liner and heat seal liner. Pack Size: 30 Tablets.

150cc heavy weight high density polyethylene (HDPE) bottles closed with 38mm polypropylene child-resistant plastic caps with a pulp liner and heat seal liner. Pack Size: 120 Tablets.

Supplier and Manufacturer

Supplier

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

This leaflet was last revised in May 2022.

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