

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
This medicine is dispensed with a doctor's prescription only

NORVIR 100 mg TABLETS

Film-coated Tablets

The active ingredient and its quantity:

Each tablet contains:
Ritonavir 100 mg

For the full list of inactive ingredients, please see section 6 “Further Information” in this leaflet.

Read this leaflet carefully in its entirety before using this medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

Norvir is used by children 2 years of age or older, adolescents and adults who are infected with HIV, the virus which causes AIDS. Norvir is not recommended for use in children 2 years of age or below.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Norvir contains the active ingredient ritonavir.

Norvir belongs to the protease inhibitor group used to control HIV infection.

Norvir medicine is administered alone or in combination with other anti-HIV medicines to control your HIV infection. The doctor will discuss with you the best combination of medicines for you.

Therapeutic group: Protease inhibitors.

2. BEFORE USING THE MEDICINE

- **Do not use the medicine if:**
 - You are sensitive (allergic) to the active ingredient or to any of the additional ingredients contained in the medicine (for the list of inactive ingredients, see section 6 “Further Information”).
 - You have severe liver disease.
 - You are currently taking any of the following medicines:
 - astemizole or terfenadine (medicines commonly used to treat allergy symptoms - these medicines may be available without prescription).
 - amiodarone, bepridil, dronedarone, encainide, flecainide, propafenone, quinidine (medicines used to correct irregular heartbeats).
 - ergotamine, dihydroergotamine (medicines used to treat migraine headache).
 - ergonovine, methylergonovine (medicines used to stop excessive bleeding that may occur following childbirth or an abortion).
 - oral (taken by mouth) midazolam, flurazepam, estazolam, clorazepate, diazepam and triazolam (medicines used to help you sleep and/or relieve anxiety).
 - pimozide, clozapine (medicines used to treat abnormal thoughts or feelings).
 - quetiapine (a medicine used to treat schizophrenia, bipolar disorder and major depressive disorder).
 - lurasidone (a medicine used to treat depression).
 - ranolazine (a medicine used to treat chronic chest pain [angina]).
 - propoxyphene, piroxicam, pethidine (medicines used to relieve pain).
 - cispapride (a medicine used to relieve certain stomach problems).
 - rifabutin (a medicine used to prevent/treat certain infections)*.
 - voriconazole (a medicine used to treat fungal infections)*.
 - lovastatin, simvastatin, lomitapide (medicines used to lower blood cholesterol).
 - neratinib (used to treat breast cancer).
 - alfuzosin (a medicine used to treat enlarged prostate gland).
 - fusidic acid (a medicine used to treat bacterial infections).
 - sildenafil, if you suffer from a lung disease called pulmonary arterial hypertension that makes breathing difficult. Patients without pulmonary arterial hypertension may use sildenafil for impotence (erectile dysfunction) under medical supervision (see “If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist” in subsection 2).
 - avanafil or vardenafil (medicines used to treat erectile dysfunction).
 - colchicine (a medicine used to treat gout), if you have kidney and/or liver problems (see “If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist” in subsection 2).
 - products containing St. John's wort (*Hypericum perforatum*), as this may stop Norvir from working properly. St. John's wort is often used in non-prescription herbal medicines.
- * Your doctor may decide that you can take rifabutin and/or voriconazole with a low dosage of Norvir (booster), but you must not take a full dosage of Norvir together with these two medicines.

If you are currently taking any of the medicines listed above, ask the doctor about switching to a different medicine while taking Norvir.

Please read the list of medicines under “If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist” in subsection 2 with regard to taking Norvir with other medicines that require special attention.

Special warnings regarding use of the medicine:
Talk to your doctor before taking Norvir.

■ Important information:

- If Norvir is taken in combination with other antiretroviral medicines, it is important that you also carefully read the patient leaflets that are provided with the other medicines. There may be additional information in those leaflets about situations when Norvir should be avoided. If you have any further questions about Norvir (ritonavir) or the other medicines prescribed, refer to the doctor or pharmacist.
- Norvir is not a cure for HIV infection or AIDS.
- People taking Norvir may still develop infections or other illnesses associated with HIV infection or AIDS. It is therefore important that you remain under the supervision of the attending doctor while taking Norvir.
- You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy. Consult the attending doctor regarding the precautionary measures necessary to prevent transmission to other people.

■ Before treatment with Norvir, inform the doctor if:
You suffer, or have suffered in the past, from:

- **A history of liver disease.**
- **Hepatitis B or C** are being treated with a combination of antiretroviral medicines, 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 that 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 an additional medicine 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 hypotension and prolonged erection.
- **Diabetes**, since there have been reports of worsening or onset of diabetes in some patients taking protease inhibitors.
- **Kidney disease**, since the doctor may need to check the dose of the other medicines you are taking (such as protease inhibitors).

■ During the course of treatment with the medicine, tell the doctor 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 Norvir can develop serious problems with their pancreas. Tell the doctor as soon as possible if this applies to you.
- **Symptoms of infection** - inform the doctor 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 the body's immune response improves and helps the body to fight these infections. In addition to the 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 the doctor immediately to seek necessary treatment.
- **Joint stiffness, aches and pains** (especially of the hip, knee and shoulder) and difficulty moving. Tell the attending doctor, 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 “**Side Effects**”).
- **Dizziness, lightheadedness, fainting spells or abnormal heartbeat**. Some patients taking Norvir may experience changes in the electrocardiogram (ECG). Tell the doctor if you have heart defects or heart rate problems (conduction defect).
- If you have any other health concerns, refer to the doctor as soon as possible.

■ Children and adolescents

Norvir is not recommended for use in children 2 years of age or below.

■ If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking:

There are some medicines that must not be taken at all together with Norvir. See the list of medicines earlier in subsection 2 “Do not use the medicine if”. There are some other medicines that can only be used under certain circumstances as described below.

The following warnings apply when Norvir is taken as a full dose. However, these warnings may also apply when Norvir is used in lower doses (a booster) with other medicines.

Tell the doctor if you are taking any of the medicines listed below, as special care should be taken:

- **Sildenafil or tadalafil** (medicines for erectile dysfunction). The dose and/or frequency of use of these medicines may need to be reduced to avoid hypotension and prolonged erection. You must not take Norvir with sildenafil if you suffer from a lung disease called pulmonary arterial hypertension (see also “**Do not use the medicine if**” in subsection 2). Tell the doctor if you are taking tadalafil for pulmonary arterial hypertension.
- **Colchicine** (a medicine for gout) as Norvir may raise the blood levels of this medicine. You must not take Norvir with colchicine if you have kidney and/or liver problems (see “**Do not use the medicine if**” in subsection 2 above).
- **Digoxin** (heart medicine). The doctor may need to adjust the dose of digoxin and monitor you in order to avoid heart problems.
- **Contraceptive medicines** (“pills”) containing ethinyl oestradiol as Norvir 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 medicines with Norvir.
- **Rosuvastatin or atorvastatin** (medicines for high cholesterol) as Norvir may raise the blood levels of these medicines. Consult your doctor before you take any cholesterol-reducing medicines with Norvir (see also “**Do not use the medicine if**” in subsection 2).
- **Steroids** (e.g., prednisolone, fluticasone propionate, dexamethasone, triamcinolone) as Norvir 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 doctor 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 Norvir.
- **Rifampicin and saquinavir** (medicines used for tuberculosis and HIV, respectively) as serious liver damage can occur when taken with Norvir.
- **Bosentan, riociguat** (medicines used for pulmonary arterial hypertension) as Norvir may increase the blood levels of these medicines.

There are medicines that must not be taken with Norvir because their effects could increase or decrease when taken together. In some cases, the doctor may request that you perform certain tests, change the dose or monitor you regularly.

This is why you should tell your doctor if you are taking any medicines, including those you have bought yourself or herbal products, but it is especially important to mention the following medicines:

- amphetamine or amphetamine derivatives;
- antibiotics (e.g., erythromycin, clarithromycin);
- anticancer treatments (e.g., abemaciclib, afatinib, apalutamide, ceritinib, encorafenib, dasatinib, ibrutinib, filotinib, 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., loratadine, fexofenadine);
- antiretroviral medicines including HIV-protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir) and non-nucleoside reverse transcriptase inhibitors (NNRTI) (delavirdine, efavirenz, nevirapine) and others (didanosine, maraviroc, raltegravir, zidovudine);
- medicines to treat tuberculosis (bedaquiline, delamanid);
- an antiviral medicine 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 for smoking cessation;
- epilepsy medicines (e.g., carbamazepine, divalproex, lamotrigine, phenytoin);
- medicines to treat heart problems (e.g., disopyramide, mexiletine and calcium channel blockers e.g., amlodipine, diltiazem, nifedipine);
- immunosuppressants (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 medicine for the treatment of gout.

There are some medicines you cannot take at all with Norvir. See the list of medicines above in subsection 2 “**Do not use the medicine if**”.

■ Use of the medicine and food

Norvir tablets should be taken with food.

■ Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, it is very important that you consult the attending doctor about this before taking this medicine.

There is extensive information on the use of ritonavir (the active ingredient in Norvir) during pregnancy. In general, pregnant women received ritonavir after the first three months of pregnancy at a lower dose (booster), along with other protease inhibitors. Norvir did not appear to increase the chance of developing birth defects compared to the general population.

Norvir can pass into breast milk. To avoid transmitting the infection, mothers with HIV must not breastfeed their children.

■ Driving and using machines

Norvir can cause dizziness. If you are affected do not drive or use machinery.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist on how to use the medicine if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.

Do not exceed the recommended dose.

Swallow the tablets whole. Do not chew, break or crush.

Take the medicine with food.

Adhere to the treatment regimen recommended by the doctor. Take Norvir every day to control your ailment, regardless of an improvement in your general feeling. If a side effect is preventing you from taking Norvir as directed, inform your doctor immediately. During episodes of diarrhoea your doctor may decide that additional monitoring is needed.

Always keep enough Norvir on hand so you do not run out. When you travel or need to stay in the hospital, make sure you have enough Norvir to last until you can get a new supply.

If you accidentally take higher dosage

If you took an overdose or if a child accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room, and bring the package of the medicine with you.

Numbness, tingling or a “pins and needles” sensation may occur if you took an overdose.

If you forget to take Norvir tablets

Take a dose as soon as you remember.

If you remembered when it is nearly time for the next dose, take the next dose only at the usual time and consult the doctor. Do not take a double dose to make up for a forgotten dose.

If you stop taking Norvir

Even if there is an improvement in your feeling, do not stop treatment with the medicine without consulting the doctor. Taking Norvir as recommended by the doctor has the best chance of delaying viral resistance to medicines.

Do not take medicines in the dark! Check the label and dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Norvir may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

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

Likewise, side effects of Norvir, when it is given with other antiretroviral medicines, depend on the additional medicines. Therefore, it is important that you carefully read the section on side effects in the leaflets provided with these other medicines.

Very common side effects (effects that occur in more than 1 user in 10):

- upper or lower stomach ache
- vomiting
- diarrhea (may be severe)
- feeling sick (nausea)
- flushing, feeling hot
- headache
- 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/tiredness
- bad taste in the mouth
- nerve damage that can cause weakness and pain
- itching
- rash
- joint and back pain

Common side effects (effects that occur in 1-10 in 100 users):

- allergic reactions including skin rashes (may be red, raised, itchy), severe swelling of the skin and other tissues
- inability to sleep (insomnia)
- 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
- seizures (fits)
- low levels of blood platelets
- thirst (dehydration)
- abnormally heavy periods
- flatulence
- loss of appetite
- mouth ulcer
- muscle aches (pain), tenderness or weakness
- fever
- weight loss
- changes in blood test results (such as blood count and blood chemistry)
- 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 (effects that occur in 1-10 in 1,000 users):

- heart attack
- diabetes
- kidney failure

Rare side effects (effects that occur in 1-10 in 10,000 users):

- 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

Side effects of unknown frequency (effects whose frequency has not yet been determined):

- kidney stones
- Tell your doctor if you are vomiting, feel sick (nauseous) or have stomach pain, because these may be signs of an inflamed pancreas. Also tell your doctor if you experience joint stiffness, aches or pains (especially of the hip, knee and shoulder) and difficulty moving, as this may be a sign of osteonecrosis. For further information, see section 2 “**Before using the medicine**”.

In patients with haemophilia type A and B, there have been reports of increased bleeding while taking this treatment or treatment with another protease inhibitor. Should this happen to you, refer immediately to the doctor.

Abnormal liver function tests, hepatitis (inflammation of the liver), and rarely jaundice, have been reported in patients taking Norvir. 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 - muscle tissue breakdown). In the event of unexplained or continual muscle pain, tenderness, weakness or cramps, stop taking the medicine, contact your doctor **as soon as possible** or go to the nearest hospital emergency room.

Refer to the doctor **as soon as possible** if you experience any symptoms that suggest an allergic reaction after taking Norvir such as: rash, hives or breathing difficulties.

If one of the side effects occurs and/or worsens or if you experience a side effect not mentioned in the list above, inform the doctor, pharmacist, the hospital emergency room, or if it is urgent, refer immediately for medical attention.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il>

5. HOW SHOULD THE MEDICINE BE STORED?

- **Avoid poisoning!** This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning.

- **Do not induce vomiting** unless explicitly instructed to do so by the doctor.

- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

- Store at a temperature below 30°C.
- Keep the Norvir tablets in their original package in order to protect from moisture.

- Do not use this medicine if you notice any discolouration.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains: **Tablet:**

Copovidone (K value 28), Anhydrous Calcium Hydrogen Phosphate, Sorbitan Laurate, Colloidal Anhydrous Silica, Sodium Stearyl Fumarate.

Tablet coating:

Hypromellose 2910 (6 mPa·s), Titanium Dioxide, Macrogols type 400, Hydroxypropyl Cellulose, Hypromellose 2910 (15 mPa·s), Talc, Macrogol Type 3350, Colloidal Anhydrous Silica, Polysorbate 80.

- What the medicine looks like and the contents of the package:
Norvir tablets - a white to cream-colored, elliptic tablet with the Abbott corporate logo debossed on one side and the code NK on the other side.

- Package size:
 - A bottle containing 30 tablets
 - A bottle containing 60 tablets

* Not all pack sizes may be marketed.

- **License holder and its address:** AbbVie Biopharmaceuticals Ltd., 4 Haharash St., Hod Hasharon, Israel.

- **Manufacturer and address:** AbbVie Deutschland GmbH & Co. KG., Knollstrasse 67061, Ludwigshafen, Germany.

- **Registration number of the medicine in the National Drug Registry of the Ministry of Health:** 148-06-33504