

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

[HA538 trade name][†]

Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600mg/200mg/300mg film-coated tablets

*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 is for you only. Do not pass it on to others. It may harm them, even if their illness seems 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 [HA538 trade name] is and what it is used for
2. What you need to know before you take [HA538 trade name]
3. How to take [HA538 trade name]
4. Possible side effects
5. How to store [HA538 trade name]
6. Contents of the pack and other information

1. What [HA538 trade name] is and what it is used for

[HA538 trade name] is an antiretroviral medicine used for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 35 kg.

[HA538 trade name] contains three active substances that are used to treat HIV infection:

- Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI)
- Tenofovir disoproxil is a nucleotide reverse transcriptase inhibitor (NtRTI)

Each of these active substances work by interfering with an enzyme (reverse transcriptase) that is essential for the virus to multiply.

[HA538 trade name] reduces the amount of virus in your body and keeps it at a very low level. It is not a cure for HIV infection but if taken correctly it will improve your immune system and reduce the risk of developing illnesses linked to HIV infection.

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

2. What you need to know before you take [HA538 trade name]

Do not take [HA538 trade name]

- if you are allergic to efavirenz, emtricitabine, tenofovir, tenofovir disoproxil or any of the other ingredients of this medicine (listed in section 6).
- if you have severe liver disease.
- if you have a heart condition, such as changes in the rhythm or rate of the heart beat, a slow heart beat, or severe heart disease.
- if any member of your family (parents, grandparents, brothers or sisters) has died suddenly due to a heart problem or was born with heart problems.
- if your health care provider has told you that you have high or low levels of electrolytes such as potassium or magnesium in your blood.
- if you are currently taking any of the following medicines:
 - astemizole or terfenadine (used to treat hay fever or other allergies)
 - bepridil (used to treat heart disease)
 - ergot alkaloids (for example, ergotamine, dihydroergotamine, ergonovine, and methylergonovine) (used to treat migraines and cluster headaches)
 - midazolam or triazolam (used to help you sleep)
 - pimozone, imipramine, amitriptyline or clomipramine (used to treat certain mental conditions)
 - elbasvir or grazoprevir (for hepatitis C infection)
 - St. John's wort (*Hypericum perforatum*) (a herbal preparation used for depression and anxiety)
 - flecainide (used to treat irregular heart beat)
 - voriconazole (used to treat fungal infections)
 - certain antibiotics (macrolides, fluoroquinolones, imidazole)
 - triazole antifungal agents
 - certain antimalarial treatments

If you are taking any of these medicines, tell your health care provider immediately. Taking these medicines with [HA538 trade name] could cause serious or life-threatening side effects or stop these medicines from working properly.

Warnings and precautions

- Talk to your health care provider before taking [HA538 trade name]. You must remain under the care of a health care provider while taking [HA538 trade name].

Tell your health care provider:

- **if you are taking other medicines** that contain efavirenz, emtricitabine, tenofovir disoproxil, tenofovir alafenamide, lamivudine or adefovir dipivoxil. [HA538 trade name] should not be taken with any of these medicines unless specifically recommended by your health care provider.
- **if you have or have had kidney disease**, or if tests have shown problems with your kidneys. [HA538 trade name] is not recommended if you have moderate to severe kidney disease.

[HA538 trade name] may affect your kidneys. Before starting treatment, your health care provider may order blood tests to assess kidney function. Your health care provider may also order blood tests during treatment to monitor your kidneys.

[HA538 trade name] is not usually taken with other medicines that can damage your kidneys (see *Other medicines and [HA538 trade name]*). If this is unavoidable, your health care provider will monitor your kidney function.

- **if you have a history of mental illness**, including depression, or of substance or alcohol abuse. Tell your health care provider immediately if you feel depressed, have suicidal thoughts or have strange thoughts (see section 4, *Possible side effects*).
- **if you have a history of convulsions (fits or seizures)** or if you are being treated with anticonvulsant therapy such as carbamazepine, phenobarbital and phenytoin. If you are taking any of these medicines, your health care provider may need to check the level of anticonvulsant medicine in your blood to ensure that it is not affected while taking [HA538 trade name]. Your health care provider may give you a different anticonvulsant.
- **if you have a history of liver disease, including chronic active hepatitis**. Patients with liver disease including chronic hepatitis B or C, who are treated with combination antiretrovirals, have a higher risk of severe and potentially life-threatening liver problems. Your health care provider may conduct blood tests in order to check how well your liver is working or may switch you to another medicine. If you have severe liver disease, do not take [HA538 trade name].
- **if you have hepatitis B infection, your health care provider will carefully consider the best treatment regimen for you**. Tenofovir disoproxil and emtricitabine, two of the active substances in [HA538 trade name], show some activity against hepatitis B virus. Symptoms of your hepatitis may become worse after discontinuation of [HA538 trade name]. Your health care provider may then conduct blood tests at regular intervals to check how well your liver is working (see section 3, *If you stop taking [HA538 trade name]*).
- **if you are over 65**. Insufficient numbers of patients over 65 years of age have been studied. If you are over 65 years of age and are prescribed [HA538 trade name], your health care provider will monitor you carefully.
- **If you have a heart disorder**, such as abnormal electrical signal called prolongation of the QT interval.

Once you start taking [HA538 trade name], look out for:

- **signs of dizziness, difficulty sleeping, drowsiness**, difficulty concentrating or abnormal dreaming. These side effects may start in the first 1 or 2 days of treatment and usually go away after the first 2 to 4 weeks.
If at any time during treatment you get problems with your balance or coordination, become confused or drowsy and unresponsive, get seizures (fits or convulsions), your speech becomes slurred or confused or you develop personality changes, you or someone close to you must let your health care provider know right away.
- **any signs of skin rash**. Rashes may be caused by [HA538 trade name]. If you see any signs of a severe rash with blistering or fever, stop taking [HA538 trade name] and tell your health care provider at once. If you had a rash while taking another NNRTI, you may be at higher risk of getting a rash with [HA538 trade name].
- **any signs of inflammation or infection**. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, 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 improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please tell your health care provider at once.

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 your health care provider immediately to seek necessary treatment.

- **bone problems.** Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe immunosuppression and higher body mass index are some of the risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your health care provider.

Bone problems (sometimes resulting in fractures) may also occur due to damage to kidney tubule cells (see section 4, *Possible side effects*).

Children and adolescents

- Do not give [HA538 trade name] to children and adolescents weighing less than 35 kg. The doses would need to be adjusted and this cannot be achieved with [HA538 trade name].

Other medicines and [HA538 trade name]

You must not take [HA538 trade name] with certain medicines. They include some common medicines and some herbal preparations (including St. John's wort) which can cause serious interactions.

Tell your health care provider if you are taking, have recently taken or might take any other medicines.

Also, [HA538 trade name] should not be taken with any other medicines that contain efavirenz (unless recommended by your health care provider), emtricitabine, tenofovir disoproxil, tenofovir alafenamide, lamivudine or adefovir dipivoxil.

Tell your health care provider if you are taking other medicines which may damage your kidneys. Some examples include:

- aminoglycosides, vancomycin (medicines for bacterial infections)
- foscarnet, ganciclovir, cidofovir (medicines for viral infections)
- amphotericin B, pentamidine (medicines for fungal infections)
- interleukin-2 (to treat cancer)
- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains)

[HA538 trade name] may interact with other medicines, including herbal preparations such as Ginkgo biloba extracts. As a result, the amounts of [HA538 trade name] or other medicines in your blood may be affected. This may stop your medicines from working properly, or may make any side effects worse. In some cases, your health care provider may need to adjust your dose or check your blood levels.

It is important to tell your health care provider if you are taking any of the following:

- **Medicines used to treat infection with the hepatitis C virus:** daclatasvir, elbasvir, grazoprevir, the combination of ledipasvir and sofosbuvir or sofosbuvir and velpatasvir.
- **Medicines used to treat bacterial infections,** including tuberculosis and AIDS-related mycobacterium avium complex: clarithromycin, rifabutin, rifampicin. Your health care provider may need to consider changing your dose or giving you an alternative antibiotic. In addition, your health care provider may consider giving you an additional dose of efavirenz to treat your HIV infection.
- **Medicines used to treat fungal infections (antifungals):** Itraconazole or posaconazole. [HA538 trade name] can reduce the amount of itraconazole or posaconazole in your blood. Your health care provider may need to consider giving you a different antifungal.

- **Medicines used to treat malaria:** Atovaquone/proguanil or artemether/lumefantrine. [HA538 trade name] may reduce the amount of atovaquone/proguanil or artemether/lumefantrine in your blood. [HA538 trade name] may also interact with other antimalarial medicines.
- **Medicines used to lower blood fats (also called statins):** Atorvastatin, pravastatin, simvastatin. [HA538 trade name] can reduce the amount of statins in your blood. Your health care provider will check your cholesterol levels and will consider changing the dose of your statin, if needed.
- **Medicines used to treat convulsions/seizures (anticonvulsants):** Carbamazepine, phenytoin, phenobarbital. [HA538 trade name] can reduce the amount of the anticonvulsant in your blood. Carbamazepine can reduce the amount of efavirenz, one of the components of [HA538 trade name], in your blood. Your health care provider may need to consider giving you a different anticonvulsant.
- **Hormonal contraceptives, such as birth control pills, an injected contraceptive, or a contraceptive implant:** You must also use a reliable barrier method of contraception. [HA538 trade name] may make hormonal contraceptives less likely to work. Pregnancies have occurred in women taking efavirenz, a component of [HA538 trade name], while using a contraceptive implant, although it has not been established that the efavirenz therapy caused the contraceptive to fail.
- **Methadone**, a medicine used to treat opiate addiction, as your health care provider may need to change your methadone dose.
- **Sertraline**, a medicine used to treat depression, as your health care provider may need to change your dose of sertraline.
- **Bupropion**, a medicine used to treat depression or to help you stop smoking, as your health care provider may need to change your dose of bupropion.
- **Diltiazem or similar medicines (called calcium channel blockers, used to treat high blood pressure).** When you start taking [HA538 trade name], your health care provider may need to adjust your dose of the calcium channel blocker.
- **Medicines used to prevent organ transplant rejection (also called immunosuppressants),** such as cyclosporine, sirolimus or tacrolimus. When you start or stop taking [HA538 trade name] your health care provider will closely monitor your plasma levels of the immunosuppressant and may need to adjust its dose.
- **Warfarin or acenocoumarol** (medicines used to reduce clotting of the blood): Your health care provider may need to adjust your dose of warfarin or acenocoumarol.
- **Ginkgo biloba extracts** (herbal preparation).

Pregnancy and breastfeeding

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

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

Driving and using machines

[HA538 trade name] may cause dizziness, impaired concentration and drowsiness. If you are affected, do not drive and do not use any tools or machines.

3. How to take [HA538 trade name]

Always take this medicine exactly as your health care provider has told you. Check with your health care provider if you are not sure.

The recommended dose is:

One tablet taken each day by mouth.

[HA538 trade name] should be taken on an empty stomach (1 hour before or 2 hours after a meal) preferably at bedtime. This may make some side effects (for example, dizziness, drowsiness) less troublesome. Swallow [HA538 trade name] whole with water.

[HA538 trade name] must be taken every day.

[HA538 trade name] should not be used in patients weighing less than 35 kg.

If your health care provider decides to stop one of the components of [HA538 trade name], you may be given efavirenz, emtricitabine and/or tenofovir disoproxil separately or with other medicines for the treatment of your HIV infection.

If you take more [HA538 trade name] than you should

If you accidentally take too many [HA538 trade name] tablets you may be at increased risk of experiencing side effects with this medicine (see section 4, *Possible side effects*). Contact your health care provider or nearest emergency department for advice. Keep the medicine with you so that you can easily describe what you have taken.

If you forget to take [HA538 trade name]

It is important not to miss a dose of [HA538 trade name].

If you miss a dose of [HA538 trade name] within 12 hours of when it is usually taken, take it as soon as you can, and then take your next dose at its regular time.

If it is almost time (less than 12 hours) for your next dose anyway, do not take the missed dose. Wait and take the next dose at the regular time. Do not take a double dose to make up for a forgotten tablet.

If you throw up within 1 hour of taking [HA538 trade name], you should take another tablet. Do not wait until your next dose is due. You do not need to take another tablet if you were sick more than 1 hour after taking [HA538 trade name].

If you stop taking [HA538 trade name]

Don't stop taking [HA538 trade name] without talking to your health care provider. Stopping this medicine can seriously affect your response to future treatment. If [HA538 trade name] is stopped, speak to your health care provider before you restart taking [HA538 trade name] tablets. Your health care provider may consider giving you the components of this medicine separately if you are having problems or need your dose to be adjusted.

When your supply of [HA538 trade name] starts to run low, get more from your health care provider. This is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The virus may then become harder to treat.

If you have both HIV infection and hepatitis B, it is especially important not to stop your [HA538 trade name] treatment without talking to your health care provider first. Some patients have had blood tests or symptoms indicating that their hepatitis has got worse after stopping emtricitabine or tenofovir disoproxil (two of the three components of this medicine). If [HA538 trade name] is stopped your health care provider may recommend that you resume hepatitis B treatment. You may require blood tests to check how your liver is working for 4 months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

Tell your health care provider immediately about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection.

If you have any further questions on the use of this medicine, ask your health care provider.

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, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects: Tell your health care provider immediately

Lactic acidosis (excess lactic acid in the blood) is a **rare** (may affect up to 1 in every 1,000 patients) but serious side effect that can be fatal. The following side effects may be signs of lactic acidosis:

- deep rapid breathing
- drowsiness
- feeling sick (nausea), being sick (vomiting) and stomach pain.

If you think you may have lactic acidosis, contact your health care provider immediately.

Other possible serious side effects

The following side effects are **uncommon** (these may affect up to 1 in every 100 patients):

- allergic reaction (hypersensitivity) that may cause severe skin reactions (Stevens-Johnson syndrome, erythema multiforme)
- swelling of the face, lips, tongue or throat
- angry behaviour, suicidal thoughts, strange thoughts, paranoia, unable to think clearly, mood being affected, seeing or hearing things that are not really there (hallucinations), suicide attempts, personality change (psychosis)
- pain in the abdomen (stomach), caused by inflammation of the pancreas
- forgetfulness, confusion, fitting (seizures), incoherent speech, tremor (shaking)
- yellow skin or eyes, itching, or pain in the abdomen (stomach) caused by inflammation of the liver
- damage to kidney tubules

Psychiatric side effects in addition to those listed above include delusions (false beliefs) and neurosis. Some patients have committed suicide. These problems tend to occur more often in those who have a history of mental illness. Always notify your health care provider immediately if you have these symptoms.

Side effects to the liver: if you are also infected with hepatitis B virus, you may experience a worsening of hepatitis after stopping treatment (see section 3).

The following side effects are **rare** (these may affect up to 1 in every 1,000 patients):

- liver failure, in some cases leading to death or liver transplant. Most cases occurred in patients who already had liver disease, but there have been a few reports in patients without any existing liver disease
- inflammation of the kidney, passing a lot of urine and feeling thirsty
- back pain caused by kidney problems, including kidney failure. Your health care provider may do blood tests to see if your kidneys are working properly
- softening of the bones (with bone pain and sometimes resulting in fractures) which may occur due to damage to the kidney tubule cells
- fatty liver

The following side effect is of unknown frequency:

- encephalopathy (brain disorder which can be severe)

If you think that you may have any of these serious side effects, talk to your health care provider.

Most frequent side effects

The following side effects are **very common** (these may affect more than 1 in 10 patients)

- dizziness, headache, diarrhoea, feeling sick (nausea), being sick (vomiting)
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions
- feeling weak

Tests may also show:

- decreases in phosphate levels in the blood
- increased levels of creatine kinase in the blood that may result in muscle pain and weakness

Other possible side effects

The following side effects are **common** (these may affect up to 1 in 10 patients)

- allergic reactions
- disturbances of coordination and balance
- feeling worried or depressed
- difficulty sleeping, abnormal dreams, difficulty concentrating, drowsiness
- pain, stomach pain
- problems with digestion resulting in discomfort after meals, feeling bloated, wind (flatulence)
- loss of appetite
- tiredness
- itching
- changes in skin colour including darkening of the skin in patches often starting on hands and soles of feet

Tests may also show:

- low white blood cell count (a reduced white blood cell count can make you more prone to infection)
- liver and pancreas problems
- increased fatty acids (triglycerides), bilirubin or sugar levels in the blood

The following side effects are **uncommon** (these may affect up to 1 in every 100 patients):

- breakdown of muscle, muscle pain or weakness
- anaemia (low red blood cell count)
- a feeling of spinning or tilting (vertigo), whistling, ringing or other persistent noise in the ears
- blurred vision
- chills
- breast enlargement in males
- decreased sexual drive
- flushing

- dry mouth
- increased appetite

Tests may also show:

- decreases in potassium in the blood
- increases in creatinine in the blood
- proteins in urine
- increased cholesterol in the blood

The breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood may occur due to damage to kidney tubule cells.

The following side effects are **rare** (these may affect up to 1 in every 1,000 patients)

- itchy rash to the skin caused by a reaction to sunlight

Reporting of side effects

If you get a side effect, talk to your health care provider. This includes side effects not listed in this leaflet. You may also be able to report such effects directly to your national reporting system if one is available. By reporting side effects, you can help to improve the available information on this medicine.

5. How to store [HA538 trade name]

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

Do not store above 30°C. Protect from light. Store in a well closed container.

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 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 [HA538 trade name] contains

- The active ingredients are 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate (TDF) equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.
- The other ingredients of [HA538 trade name] are microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, hydroxypropyl cellulose, magnesium stearate, polyvinyl alcohol (partly hydrolysed), titanium dioxide, macrogol/PEG, talc, iron oxide red and iron oxide black.

What [HA538 trade name] looks like and contents of the pack

Pink coloured, capsule-shaped, film-coated tablets debossed with “128” on one side and “H” on the other side.

A white opaque HDPE bottle with fitted with white polypropylene 38mm child resistant plastic caps with pulp liners and 2.0 g of silica gel desiccant.

Pack size: 28 or 30 tablets

A white opaque HDPE bottle fitted with white polypropylene 53 mm child resistant plastic caps with pulp liners and 2.0 g of silica gel desiccant.

Efavirenz/emtricitabine/tenofovir disoproxil fumarate
600mg/200mg/300mg film-coated tablets
(Hetero Labs Limited) HA538

WHOPAR Part 3

March 2023

Pack size: 500 tablets

Supplier and Manufacturer

Supplier

Hetero Labs Limited
Hetero Corporate, 7-2-A2
Industrial Estates
Sanath Nagar, Hyderabad
Telangana, 500 018
India.
Tel. : +91 40 23704923/ 24/25
Fax : +91 40 23714250 / 2370 4926
Email: contact@heterodrugs.com

Manufacturer

Hetero Labs Limited
Unit – V Sy No. 439, 440, 441 & 458
TSIC Formulation SEZ
Polepally village, Jadcherla Mandal
Mahaboob Nagar District
Telangana
India.

For any information about this medicine, contact the supplier.

This leaflet was last revised in March 2023

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