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

[HA707 trade name][†]
Dolutegravir (sodium)/lamivudine/tenofovir disoproxil fumarate

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 [HA707 trade name] is and what it is used for

[HA707 trade name] is a medicine used to treat HIV (human immunodeficiency virus) infection in adults and adolescents who weigh at least 30 kg. It contains three active ingredients: dolutegravir, lamivudine and tenofovir disoproxil. Dolutegravir belongs to a group of antiretroviral medicines called integrase inhibitors. Tenofovir is a nucleotide reverse transcriptase inhibitor, while lamivudine belongs to the group of the nucleoside analogue reverse transcriptase inhibitors.

[HA707 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.

[HA707 trade name] does not work equally well in everybody. Your health care provider will check how well your treatment is working.

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 [HA707 trade name]

Do not take [HA707 trade name] if you are:

- allergic to dolutegravir, tenofovir disoproxil, lamivudine or any of the other ingredients of this medicine (listed in section 6)

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

- taking medicines such as dofetilide (to treat heart conditions) or fampridine (also known as dalfampridine used in multiple sclerosis).

If you think any of these apply to you, tell your health care provider.

Warnings and precautions

Look out for important symptoms

Some people taking medicines for HIV infection develop other conditions, which can be serious. These include:

- infections and inflammation
- joint pain, stiffness and bone problems

You need to know about important signs and symptoms to look out for while you are taking [HA707 trade name].

Tell your healthcare provider about any flu-like illness – either in the month before starting [HA707 trade name], or at any time while taking [HA707 trade name].

Read the information, 'Other possible side effects' in Section 4 of this leaflet.

Kidney disease

[HA707 trade name] may affect your kidneys. Before starting this medicine you may need blood tests to check how well your kidneys are working. Blood tests may also be required during treatment to check the health of your kidneys.

Tell your health care provider if you have had kidney disease or if tests have shown problems with your kidneys. If so, the dose of tenofovir disoproxil and lamivudine may need to be reduced. In such cases formulations of tenofovir disoproxil and lamivudine other than [HA707 trade name] should be used.

[HA707 trade name] is not usually taken with other medicines that can damage your kidneys (see "Other medicines and [HA707 trade name]."). If this is unavoidable, you may need regular tests to check how well your kidneys are working.

Liver disease

Tell your health care provider if you have a history of liver disease, including hepatitis. HIV-infected patients with liver disease, including chronic hepatitis B or C, who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you are infected with HIV and hepatitis B virus, your health care provider will carefully consider the best treatment for you. If you have a history of liver disease or chronic hepatitis B infection your health care provider may conduct blood tests to monitor your liver function.

Children

[HA707 trade name] is suitable only for adolescents who weigh at least 30 kg. Other medicines that contain smaller amounts of dolutegravir, tenofovir or lamivudine are needed for patients who weigh less than 30 kg.

Other medicines and [HA707 trade name]

Tell your health care provider if you are taking, have recently taken or are planning to take any other medicines. This includes medicines that you buy without a prescription and herbal medicines.

You **must not** take [HA707 trade name] with dofetilide, which is used to treat heart conditions or fampridine (used in treatment of multiple sclerosis).

Some medicines can affect how [HA707 trade name] works or increase side effects. [HA707 trade name] can also affect how some other medicines work.

Tell your health care provider if you are taking any of the following:

- metformin, to treat diabetes

- antacids, to treat indigestion and heartburn. Do not take an antacid during the 6 hours before you take [HA707 trade name], or for at least 2 hours after you take it
- calcium supplements, iron supplements and multivitamins. Do not take a calcium supplement, iron supplement or multivitamin during the 6 hours before you take [HA707 trade name], or for at least 2 hours after you take it
- didanosine, etravirine, efavirenz, fosamprenavir/ritonavir, nevirapine or tipranavir/ritonavir, to treat HIV infection
- rifampicin or rifapentine to treat tuberculosis and other bacterial infections
- phenytoin and phenobarbital, to treat epilepsy
- oxcarbazepine and carbamazepine, to treat epilepsy or bipolar disorder
- St John's wort (*Hypericum perforatum*), a herbal remedy used for treating depression
- other medicines containing tenofovir disoproxil, emtricitabine, lamivudine or zalcitabine to treat HIV infection

It is very important to tell your health care provider if you are taking other medicines that may damage your kidneys. These include:

- aminoglycosides, pentamidine or vancomycin (for bacterial infection)
- amphotericin B (for fungal infection)
- foscarnet, ganciclovir, or cidofovir (for viral infection)
- adefovir dipivoxil (for hepatitis B virus infection)
- tacrolimus (for suppression of the immune system)
- interleukin-2 (to treat cancer)
- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains) such as aspirin and ibuprofen.

If you are taking any of these, your health care provider may adjust your dose or arrange extra check-ups.

Other medicines containing didanosine (for HIV infection):

Taking [HA707 trade name] with medicines that contain didanosine can increase the amount of didanosine in your blood. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), sometimes causing death, has been reported when medicines containing tenofovir disoproxil and didanosine were taken together. Combining tenofovir disoproxil with didanosine can also reduce the effects of antiretroviral therapy. Your health care provider will carefully consider whether to treat you with a combination of tenofovir disoproxil and didanosine.

If you are taking another antiviral medicine called a protease inhibitor to treat HIV, your healthcare provider may order blood tests to closely monitor your kidney function.

It is also important to tell your health care provider if you are taking ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir to treat hepatitis C infection.

Pregnancy

If you are pregnant, if you become pregnant, or if you are planning to have a baby talk to your health care provider about the risks and benefits of taking [HA707 trade name]. Your health care provider will review your treatment.

Taking [HA707 trade name] around the time you become pregnant or during the first weeks of pregnancy, may increase the risk of a type of birth defect, called neural tube defect (e.g. spina bifida).

Do not stop taking [HA707 trade name] without checking with your health care provider, as this may harm you and your unborn baby.

Breast-feeding

If you wish to breast-feed your baby, you should discuss the risks and benefits with your health care provider.

Driving and using machines

[HA707 trade name] can make you dizzy and have other side effects that make you less alert. Do not drive or operate machinery until you are sure that you do not have side effects that affect driving or using machines.

Excipients

[HA707 trade name] contains mannitol which may have a mild laxative effect. This medicine also contains lactose. If your health care provider has told you that you have an intolerance to some sugars, contact your health care provider before you take this medicine.

3. How to take [HA707 trade name]

Always take [HA707 trade name] exactly as your health care provider has told you. Do not stop taking it without checking with your health care provider. Check with the health care provider if you are not sure.

You can take [HA707 trade name] with food or between meals.

Adults and adolescents

The dose of [HA707 trade name] in adults and adolescents weighing at least 30 kg is one tablet once a day.

Adults whose HIV infection is resistant to medicines similar to dolutegravir, one of the components of [HA707 trade name], may be given additional doses of medicines containing the active substance dolutegravir only.

Adolescents whose HIV infection is resistant to medicines similar to dolutegravir, one of the components of [HA707 trade name], should **not** take [HA707 trade name].

Children

[HA707 trade name] is not suitable for children weighing less than 30 kg and different formulations should be used.

Antacids, calcium supplements, iron supplements, multivitamins

Ask your health care provider for advice if you are taking:

- an antacid (a medicine used for treating indigestion and heartburn).
- calcium supplements
- iron supplements
- multivitamins.

Take these medicines at least 6 hours before you take [HA707 trade name] or take [HA707 trade name] at least 2 hours after taking an antacid, calcium or iron supplement, or multivitamins.

If you take more [HA707 trade name] than you should

If you take too many tablets of [HA707 trade name], contact your health care provider for advice. If possible, show them the [HA707 trade name] pack.

If you forget to take or if you vomit after taking [HA707 trade name]

If you forget to take a dose, take the missed dose as soon as you remember on the same day. If you do not remember on the same day, take the normal dose on the next day. Do not take a double dose to make up for forgotten dose. If you are unsure about what to do, ask your health care provider.

If you vomit within 1 hour of taking [HA707 trade name], then you should take an extra dose. If vomiting occurs more than an hour after taking the dose, then you do not need to take an extra dose and can take the next dose as usual when it is due.

Don't stop taking [HA707 trade name] without advice from your health care provider

Take [HA707 trade name] for as long as your health care provider recommends it. Don't stop unless your health care provider advises you to. Taking the tablets regularly is very important because the amount of virus may start to increase if the medicine is stopped for even a short time. The infection may then become harder to treat.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects but not everybody gets them.

Talk to your health care provider if there is any worsening of your health. The changes could be caused by the medicine or the condition getting worse.

Allergic reactions

See a health care provider straightaway if you get an allergic reaction because the health care provider may decide that you should stop taking [HA707 trade name]. The signs of allergic reactions are:

- skin rash
- fever
- tiredness (fatigue)
- swelling under the skin which can involve the face or mouth and difficulty in breathing
- muscle and joint ache

Very common side effects

These may affect more than 1 in 10 people

- rash
- headache
- lack of energy (asthenia)
- dizziness
- diarrhoea
- feeling sick (nausea) and vomiting

Tests may also show:

- abnormally low levels of phosphate in the blood

Common side effects

These may affect up to 1 in 10 people:

- cough, nasal symptoms
- tiredness
- hair loss
- fever
- itching (pruritus)
- muscle disorders and joint ache (arthralgia)
- abdominal (belly) pain and discomfort,

- wind (flatulence)
- difficulty sleeping (insomnia), abnormal dreams
- depression
- anxiety

Tests may also show:

- liver problems (increase in liver enzymes)
- increase in an enzymes produced in the muscle called creatine phosphokinase

Uncommon side effects

These may affect up to 1 in 100 people:

- yellow skin or eyes, itching, or pain in the abdomen (tummy) caused by inflammation of the liver (hepatitis)
- muscle pain (myalgia) and muscle weakness
- breakdown of muscle fibres (rhabdomyolysis)
- panick attack
- suicidal thoughts and behaviours (particularly in patients who have had depression or mental health problems before)
- allergic reactions
- appearance of symptoms of infection as part of the 'immune reactivation syndrome' (see Warnings and precautions)

Tests may also show

- increased creatinine in your blood
- a decreased number of cells involved in blood clotting (thrombocytopenia)
- a low red blood cell count (anaemia) or low white blood cell count (neutropenia)

Rare side effects

These may affect up to 1 in 1000 people:

- pain in the tummy (abdomen) caused by inflammation of the pancreas
- lactic acidosis (excess of lactic acid in the blood)
- liver failure
- fatty liver
- swelling under the skin (angioedema)
- inflammation of the kidney, passing a lot of urine and feeling thirsty
- changes to your urine and back pain caused by kidney problems, including kidney failure
- softening of the bones (with bone pain and sometimes resulting in fractures)
- muscle disease causing weakness (myopathy)

Tests may also show

- damage to kidneys
- increase in an enzyme called amylase (pancreas problems)

Lactic acidosis (excess lactic acid in the blood) is a **rare** 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

Very rare side effects

These may affect up to 1 in 10000 people

- nerve injury causing weakness and sensations of tingling, pricking, or numbness of the skin, especially in the feet and hands (peripheral neuropathy)
- a failure of the bone marrow to produce new red blood cells (pure red cell aplasia)

Tests may also show:

- damage to kidney tubule cells

Side effects with unknown frequency

- death of bone tissue (osteonecrosis)
- decreases in potassium in the blood

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

Symptoms of infection and inflammation

People with advanced HIV infection (AIDS) have weak immune systems, and are more likely to develop serious infections (opportunistic infections). Such infections may have been 'silent' and not detected by the weak immune system before treatment was started. After starting treatment, the immune system becomes stronger, and may attack the infections, which can cause symptoms of infection or inflammation. Symptoms usually include fever, plus some of the following:

- headache
- stomach ache
- difficulty breathing.

In rare cases, as the immune system becomes stronger, it can also attack healthy body tissue (autoimmune disorders). The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection. Symptoms may include:

- palpitations (rapid or irregular heartbeat) or tremor
- hyperactivity (excessive restlessness and movement)
- weakness beginning in the hands and feet and moving up towards the trunk of the body.

If you get any symptoms of infection and inflammation or if you notice any of the symptoms above, tell your healthcare provider immediately. Don't take other medicines for the infection without your health care provider's advice.

Joint pain, stiffness and bone problems

Some people taking combination therapy for HIV develop a condition called osteonecrosis. With this condition, parts of the bone tissue die because of reduced blood supply to the bone. People may be more likely to get this condition:

- if they have been taking combination therapy for a long time
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if they are overweight.

Signs of osteonecrosis include:

- stiffness in the joints
- aches and pains in the joints (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms, tell your health care provider.

Weight, blood lipid and blood glucose 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 lifestyle, and in the case of blood lipids sometimes to the HIV medicines themselves. Your health care provider will test for these changes.

If you get any side effects, talk to your health care provider. This includes any possible side effects not listed in this leaflet.

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 [HA707 trade name]

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

Keep the bottle tightly closed. Do not remove desiccant.

Do not store above 30ºC. Store in the original container.

Discard the product 90 days after first opening.

Do not use this medicine after the expiry date stated on the label 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.
Keep this medicine out of the sight and reach of children.

What [HA707 trade name] contains

- The active substances are dolutegravir (as sodium), lamivudine and tenofovir disoproxil fumarate. Each tablet contains 50mg dolutegravir (as sodium), 300mg lamivudine and tenofovir Disoproxil Fumarate 300 mg equivalent to tenofovir disoproxil 245 mg.

- The other ingredient(s) of [HA707 trade name] are excipients:-
  Core tablet: Mannitol, Microcrystalline cellulose, Sodium starch glycolate, Povidone K30, Lactose monohydrate, Pregelatinized starch, Croscarmellose sodium and Sodium stearyl fumarate

  Film coat: Polyvinyl alcohol, Titanium dioxide, Macrogol/polyethylene glycol, and Talc

What [HA707 trade name] looks like and contents of the pack

White coloured, oval shaped, biconvex film coated tablet debossed with 'LA75' on one side and plain on the other side.

No score-line.

White HDPE bottle with 1g silica gel canister and closed with polypropylene child resistant closure with induction sealing wad. Pack sizes: 30 and 90 tablets

White HDPE bottle with 2g silica gel canister and closed with non-child resistant closure with induction sealing wad. Pack size: 180 tablets

Supplier and Manufacturer

Supplier

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"*For any information about this medicinal product, please contact the supplier*"

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