WHO-PQ RECOMMENDED PATIENT INFORMATION LEAFLET

This patient information leaflet focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities (term to be revised).
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

Information for the patient

[HA629 trade name]*
Lamivudine /Nevirapine /Zidovudine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have questions about the medicine, ask your health care provider.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness seem to be the same as yours.
- If you get any side effects, talk to your health care provider.This includes unwanted effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [HA629 trade name] is and what it is used for
2. What you need to know before you take [HA629 trade name]
3. How to take [HA629 trade name]
4. Possible side effects
5. How to store [HA629 trade name]
6. Contents of the pack and other information

1. What [HA629 trade name] is and what it is used for

[HA629 trade name] contains lamivudine, zidovudine and nevirapine. These medicines are antiviral medicines, also known as antiretrovirals, belonging to the following two groups: nucleoside analogues (NRTIs, lamivudine and zidovudine) and non-nucleoside reverse transcriptase inhibitors (NNRTIs, nevirapine). These are used to treat Human Immunodeficiency Virus (HIV) infection.

[HA629 trade name] is used as antiretroviral combination therapy for the treatment of HIV infection in adults and in children that weigh at least 25 kg.

The three medicines contained in [HA629 trade name] can be used separately with other medicines for combination treatment of HIV infection or can be used together. The dose of each active ingredient in [HA629 trade name] is the same as that recommended for the medicines when used separately. Treatment with [HA629 trade name] will only be instituted by your health care provider, when you have been shown to be stable on the three individual compounds. [HA629 trade name] reduces the amount of HIV in your body, and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infections. Response to treatment with [HA629 trade name] varies between patients. Your health care provider will be monitoring the effectiveness of your treatment.

[HA629 trade name] may improve your condition, but it is not a cure for your HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with [HA629 trade name] has not been shown to eliminate the risk of passing HIV infection on to others by sexual contact or by blood transfer. Therefore, you must continue to take appropriate precautions to avoid giving the virus to others.

*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 [HA629 trade name]

Do not take [HA629 trade name]:

- if you are hypersensitive (allergic) to lamivudine, zidovudine, nevirapine or any of the other ingredients of [HA629 trade name] (see section 6, "What [HA629 trade name] contains"),
- if you have very low red blood cell count (severe anaemia) or very low white blood cell count (neutropenia).
- if you have permanent liver disease or marked changes in liver function,
- if you previously experienced liver inflammation, severe skin rash or liver injury while on treatment with nevirapine-containing products.
- Patients taking [HA629 trade name] must not take products containing rifampicin or St. John's wort *(Hypericum perforatum*) as this may stop [HA629 trade name] from working properly.

Warnings and precautions

Before using [HA629 trade name], you should have told your health care provider:
• if you have ever had or still have a liver disease (such as hepatitis),
• if you are suffering from or have ever suffered from kidney disease.

It is important that your health care provider knows about all your symptoms even when you think they are not related to HIV infection. Your health care provider may decide to prescribe lamivudine, zidovudine and/or nevirapine as separate medicines instead of [HA629 trade name].

Liver disease
During the first 10 to 12 weeks of treatment with [HA629 trade name] your health care provider will closely monitor you for the occurrence of severe and life-threatening skin reactions and serious hepatic injuries.

As [HA629 trade name] may cause changes in liver function, your health care provider will monitor the function of your liver by blood tests before and at regular intervals during treatment with [HA629 trade name]. Patients with chronic hepatitis B or C and treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require additional blood tests for control of liver function.

You are at higher risk of severe and potentially fatal liver damage:
- if you already have raised liver function tests,
- if you have Hepatits B or C co-infection,
- if you are female,
- if you are not already receiving effective treatment of HIV infection.

If any of these risk factors applies to you, your health care provider will monitor you more closely.

- if you have higher CD4 cell counts at the start of treatment with any nevirapine-containing product.

Therapy with any nevirapine-containing product should not be started in women with CD4 cell counts greater than 250cells/mm^3 or in men with CD4 cell counts greater than 400 cells/mm^3, unless HIV is already well-treated by other drugs, and there is a switch to nevirapine, or if the benefit is considered to outweigh the risk.

If you develop clinical symptoms suggesting an injury of the liver, such as loss of appetite, nausea, jaundice (yellowing of the skin and eye white), dark urine, discoloured stools, pain and tenderness in the upper right abdomen, you should discontinue taking [HA629 trade name] and must contact your health care provider immediately.

If you have a chronic hepatitis B infection, you should not stop your treatment without instructions from your health care provider, as you may have a recurrence of your hepatitis. This recurrence may be more severe if you have serious liver disease.

Blood disorders
Since low red blood cell count (anaemia) as well as low white blood cell count (neutropenia/leucopenia) may occur due to treatment with [HA629 trade name], regular blood tests will be arranged to check whether there is a problem.

Skin reactions
[HA629 trade name] may cause skin reactions and allergic reactions, which in the worst case can be serious and life-threatening. Fatalities have been reported. Such reactions may appear in form of rash accompanied by other side effects such as fever, blistering, mouth sores, eye inflammation, facial swelling, general swelling, muscle or joint aches, a reduction in white blood cells (granulocytopenia), general feelings of illness or severe problems with liver or kidneys. If you experience a severe rash or any rash associated with other side effects of a hypersensitivity reaction, you should discontinue taking [HA629 trade name] right away and must contact your health care provider immediately.

If you develop severe liver, skin or allergic reactions while taking [HA629 trade name], never take [HA629 trade name] or any other nevirapine-containing product again without asking your health care provider.

Lactic acidosis
Females, particularly if very overweight, and patients with liver disease may be more at risk of getting a rare, but serious side effect called lactic acidosis, a build up of lactic acid in the body. If lactic acidosis occurs, it usually develops after a few months of treatment. Deep rapid breathing, drowsiness, and non specific symptoms such as nausea, vomiting and stomach pain, might indicate the development of this condition (see section 4, “Possible side effects”). While you are being treated with [HA629 trade name] your health care provider will monitor you for any signs that you may be developing lactic acidosis.

Immune reactivation syndrome
In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, inform your health care provider immediately.

Bone problems
Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue). Your risk of developing this disease may be higher, e.g. when your immune system is severely compromised or when you drink alcohol regularly.
If you notice joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement, inform your health care provider.

You will need to take [HA629 trade name] every day. This medicine helps to control your condition, but it is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease (e.g. opportunistic infections). These will require specific and sometimes preventive treatment. You should keep in regular contact with your health care provider. Do not stop taking your medicine without first talking to your health care provider.

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

Other medicines and [HA629 trade name]

Please tell your health care provider if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of [HA629 trade name], or [HA629 trade name] may affect their action.

[HA629 trade name] must not be taken with rifampicin.
[HA629 trade name] must not be taken with herbal preparations containing St. John’s Wort.

[HA629 trade name] should not be taken with the following agents:
- stavudine, emtricitabine, efavirenz, several protease inhibitors (e.g. tipranavir/rtv, atazanavir/rtv, fosamprenavir, indinavir), ribavirin (antiviral agents),

- ketoconazole, itraconazole (antifungals),
- probenecid (uric acid lowering agent).

[HA629 trade name] may also interact with the following medicines and may make any side effects worse or may impact on the other agent's efficacy:
- oral contraceptives ("the pill"). Therefore, you should employ an alternative contraceptive method such as barrier contraception (e.g. condoms), if you are taking [HA629 trade name].
- fluconazole (antifungal medicine),
- clarithromycin, rifabutin (antibiotics),
- artemisinins, amodiaquine/artesunate, quinine, lumefantrine, halofantrine, atovaquone (antimalarials),
- phenytoin, valproic acid (anticonvulsants),
- warfarin (medicine for prophylaxis of blot clots),
- doxorubicin (anti-cancer medicine).

[HA629 trade name] with food and drink

[HA629 trade name] may be taken with or without food.

Pregnancy and breast-feeding

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 antiretroviral therapy to you and your child.
If you have taken [HA629 trade name] during your pregnancy, your health care provider may request regular visits to monitor the development of your child. Such visits may include blood tests and other diagnostic tests.
In children whose mothers took nucleoside and nucleotide analogues during pregnancy, the benefit of the reduced risk of being infected with HIV is greater than the risk of suffering from side effects.

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

Driving and using machines

[HA629 trade name] may cause side effects such as drowsiness or headache that can impair your ability to drive and to use machines.

Important information about some of the ingredients of [HA629 trade name].

[HA629 trade name] contains lactose. If your health care provider has told that you have an intolerance to some sugars, contact your health care provider before taking [HA629 trade name].

3. How to take [HA629 trade name]

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

The recommended dose of [HA629 trade name] in adults and children with a body weight of 25 kg or more is one tablet twice daily.

Tablets should be swallowed whole and neither be split nor crushed

Children:
[HA629 trade name] is not indicated for children weighing less than 25 kg, since appropriate dose reductions cannot be made.

Dose adjustments:
If your dose of [HA629 trade name] needs to be reduced, for example if you have kidney problems or discontinuation of therapy with one of the active substances of [HA629 trade name] is necessary, then your

medicine may be changed to separate preparations of lamivudine, zidovudine and nevirapine, which are available as tablets/capsules and liquid formulations for oral use.

The tablets can be taken with or without food.

If you take more [HA629 trade name] than you should

If you have taken too many tablets or if someone accidentally swallows some, there is no immediate danger. However, you should contact your health care provider or the nearest hospital emergency department for further advice.

If you forget to take [HA629 trade name]

If you accidentally miss a dose and notice within 6 hours take the missed dose as soon as possible. Take the next regular dose as scheduled. If you notice later, then simply take your normal dose when the next one is due. Do not take a double dose to make up for forgotten individual doses.

If you stop taking [HA629 trade name]

Because your medicine controls and does not cure your condition, you will normally need to take it continuously. You should not stop treatment unless your health care provider tells you to.
If you have any further questions on the use of this product, ask your health care provider.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by [HA629 trade name], and those caused by any other medicines you may be taking at the same time, and by the HIV disease. For this reason, it is important that you inform your health care provider of any change in your health.

The major side effects of [HA629 trade name] are severe and life-threatening cutaneous reactions and serious hepatic injuries. These occur mainly in the first 10 to 12 weeks of treatment with [HA629 trade name]. This is therefore an important period which requires close surveillance (see section 2, "Warnings and precautions").

The most *commonly* reported (greater than 1 in every 100 patients treated) side effects are hypersensitivity reactions (including general weakness, low blood pressure, hives and swelling of the face), fatigue, headache, nausea, vomiting, stomach pain, diarrhoea, fever, rash (red, raised or itchy), increase in certain liver enzymes muscle pain and other muscle disorders, dizziness, cough, nasal symptoms, tiredness, difficulty sleeping, hair loss, anaemia (low red blood cell count) and neutropenia (low white blood cell count). If the number of red blood cells is reduced, you may have symptoms of tiredness or breathlessness and a reduction in your white blood cell count can make you more prone to infections.

The following side effects are *uncommon* (between 1 in 1000 and 1 in 100 patients treated): flatulence, breathlessness, general aches and pains, joint pain, and decrease of platelets (blood cells important for blood clotting). If you have a low platelet count you may notice that you bruise more easily.

There are *rare* reports (between 1 in 10 000 and 1 in 1000 patients treated) of patchy colour changes inside the mouth, nail and skin colour changes, a blood disorder called pure red cell aplasia, heartburn, chest pain (possibly indicating a heart muscle disease called cardiomyopathy), breakdown of muscle tissue, liver disorders such as enlarged liver, fatty liver, inflammation of the liver (hepatitis), inflammation of the pancreas, sweating, flu-like feeling, drowsiness, passing urine more frequently, breast enlargement in male patients, chest pain, chills, loss of appetite, taste changes, tingling in the limbs, convulsions, inability to concentrate, depression and feeling anxious, a build-up of lactic acid in the body known as lactic acidosis (see section 2, "What you need to know before you take [HA629 trade name]").

Very rarely (in less than 1 in 10 000 patients treated) a blood disorder called aplastic anaemia has been reported.

Frequency *not known*:

Combination antiretroviral therapy may also cause raised sugar in the blood, resistance to insulin and diabetes (see section 2, "What you need to know before you take [HA629 trade name]").

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and around internal organs, breast enlargement and fatty lumps on the back of the neck ('buffalo hump'). The cause and long-term health effects of these conditions are not known at this time.

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 (see section 2, "Warnings and precautions").

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (the death of bone tissue caused by loss of blood supply to the bone). Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in moving (see section 2, "Warnings and precautions").
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your health care provider as soon as possible.

Reporting of side effects
If you get any side effects,talk to your health care provider.This includes unwanted effects not listed in this leaflet.If available, you can also report side effects directly through the national reporting system. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [HA629 trade name]

Do not store above 30°C.

Blister pack:
Store tablets in the blisters in the provided carton.

HDPE bottle:
Keep the bottle tightly closed.

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

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.

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 [HA629 trade name] contains

The active substances are lamivudine, nevirapine and zidovudine.

The other ingredients are :
Core tablet: lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, povidone, colloidal silicon dioxide and magnesium stearate.
Film coat: hypromellose, titanium dioxide, macrogol/PEG and polysorbate.

What [HA629 trade name] looks like and contents of the pack

White to off-white coloured, capsule-shaped, bevelled edged, biconvex, film-coated tablet, debossed with 'I' on one side and '47' on other side.

Blister pack
[HA629 trade name] is available in PVC/PVDC-Alu blister packs.
Each blister contains 10 tablets. Such six blisters are packed in a carton.

Bottle pack
[HA629 trade name] is also available in bottles of 60 tablets.
The container is a white opaque HDPE bottle closed with a white polypropylene child-resistant cap.

Supplier
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Manufacturer
Micro Labs Limited
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Verna Industrial Estate, Verna, Salcette
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For any information about this medicine, contact the supplier:

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This leaflet was last revised in November 2019

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