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

[HA433 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 [HA433 trade name] is and what it is used for

[HA433 trade name] contains lamivudine, zidovudine and nevirapine. These medicines are antiviral medicines, also known as antiretrovirals, belonging to two groups referred to as nucleoside analogues (NRTIs, lamivudine and zidovudine) and non-nucleoside reverse transcriptase inhibitors (NNRTIs, nevirapine). These are medications used to treat Human Immunodeficiency Virus (HIV) infection.

[HA433 trade name] is used as antiretroviral combination therapy for the treatment of HIV infection. The three medicines contained in [HA433 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 [HA433 trade name] is the same as that recommended for the medicines when used separately. [HA433 trade name] reduces the amount of HIV in the body, and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cells that play an important role in maintaining a healthy immune system to help fight infections. Response to treatment with [HA433 trade name] varies between patients. Your child's health care provider will be monitoring the effectiveness of your child's treatment.

[HA433 trade name] should improve your child's condition, but it is not a cure for the HIV infection. HIV infection is spread by contact with blood or sexual contact with an infected individual. Treatment with [HA433 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/ your child must continue to take appropriate precautions to avoid giving the virus to others.

This product is intended for use in children, however safety information regarding use in adults is also provided in this leaflet.

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

2. What you need to know before you give [HA433 trade name]

Your child should not be given [HA433 trade name]:

- if he/she is allergic (hypersensitive) to lamivudine, zidovudine, nevirapine or any of the other ingredients of [HA433 trade name] listed at the end of this leaflet. If this applies to your child, tell your child's health care provider immediately and don't give [HA433 trade name] to your child.
- if he/she has a very low red blood cell count (severe anaemia) or very low white blood cell count (neutropenia)
- if he/she has serious liver disease or marked changes in liver function
- if he/she previously experienced liver inflammation, severe skin rash or liver injury while on treatment with nevirapine-containing products
- patients taking [HA433 trade name] must not take products containing rifampicin or St. John's wort *(Hypericum perforatum*, a herbal remedy against depression) as this may prevent [HA433 trade name] from working properly.

Warnings and precautions

Before using [HA433 trade name] you should have told the health care provider:

• if your child has ever had or still has a liver disease (such as hepatitis)

• if your child is suffering from or has ever suffered from kidney disease.

It is important that the health care provider knows about all your child's symptoms, even when you think they are not related to HIV infection. The health care provider may decide to prescribe lamivudine, zidovudine and/or nevirapine as separate medicines instead of [HA433 trade name].

Liver disease

During the first 18 weeks of treatment with medicines containing nevirapine, such as [HA433 trade name] the health care provider will closely monitor your child for the possible occurrence of severe and life-threatening skin reactions and serious liver problems.

Since [HA433 trade name] may cause changes in liver function, the health care provider will monitor the function of your child's liver by blood tests before and at regular intervals during treatment with [HA433 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 to monitor their liver function.

- if one already has abnormally increased liver function tests - if one also has Hepatits B or C infection - if one is female. - if one has higher CD4 cell counts at the start of treatment with any nevirapine-containing product. If any of these possible risk factors applies to your child, the health care provider will monitor your child more closely.

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 the benefits are considered to outweigh the risk.

If your child develops clinical symptoms suggesting damage to the liver, such as loss of appetite, nausea, jaundice (yellowing of the skin and whites of the eyes), dark urine, discoloured stools (faeces), or pain and tenderness in the upper right abdomen, you should immediately stop giving [HA433 trade name] to him/her and you must contact the health care provider immediately.

If your child has a chronic hepatitis B infection, you should not stop his/her treatment without instructions from the health care provider, or your child's hepatitis may recur. This recurrence may be more severe if your child has 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 [HA433 trade name], regular blood tests will be arranged to check whether there is a problem.

Skin reactions
[HA433 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 the form of a 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 your child experiences a severe rash or any rash associated with other side effects of an allergic reaction, as described above, you should stop giving him/her [HA433 trade name] right away and must contact the health care provider immediately.

If your child develops severe liver, skin or allergic reactions while taking [HA433 trade name] he/she should never take [HA433 trade name] or any other nevirapine-containing product again without asking the health care provider.

Fat distribution
Redistribution, accumulation or loss of body fat may occur in patients receiving combination antiretroviral therapy. Contact the health care provider if you notice changes in your child's body shape.

Lactic acidosis
Women, particularly if very overweight and patients with liver disease may be at greater risk of developing 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 may indicate the development of this condition (see section 3). While your child is being treated with [HA433 trade name] the health care provider will monitor you for any signs that he/she might be developing lactic acidosis.

Immune reactivation syndrome
In some patients with advanced HIV infection (AIDS) and a history of AIDS-associated (opportunistic) infections, signs and symptoms of inflammation from such 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 without obvious symptoms. If you notice any symptoms of infection in your child, inform the health care provider immediately.

Bone problems
Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue). The risk of developing this disease may be higher if the immune system is severely weakened, or when drinking alcohol regularly.
So far, this disease has been reported mainly in adults. However, if your child notices joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement, inform the health care provider.

General
Your child will need to take [HA433 trade name] every day. This medicine helps to control your child's condition, but it is not a cure for HIV infection. Your child 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 the health care provider. Do not stop giving the medicine to your child without first talking to the health care provider.
Your child 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 [HA433 trade name]

Tell the health care provider if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of [HA433 trade name], or [HA433 trade name] may affect their action.

[HA433 trade name] must not be taken with rifampicin.
[HA433 trade name] must not be taken with herbal preparations containing St. John's Wort.

[HA433 trade name] should not be taken with the following agents:

- other medicinal products containing lamivudine to treat hepatitis B infection
- 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)

[HA433 trade name] may also interact with the following medicines and may make any side effects worse or may affect the other medication's effectiveness:
- oral contraceptives ("the pill"). Therefore, one should employ an alternative contraceptive method such as barrier contraception (e.g. condoms) while taking [HA433 trade name]
- fluconazole (antifungal medicine)
- clarithromycin, rifabutin (antibiotics)
- artemisinins, amodiaquine/artesunate, quinine, lumefantrine, halofantrine, atovaquone (antimalarials)
- phenytoin, valproic acid (anticonvulsants)
- warfarin (medicine for preventing blood clots)
- doxorubicin (anti-cancer medicine)

Taking [HA433 trade name] with food and drink

[HA433 trade name] may be taken with or without food.

Pregnancy and breast-feeding

Ask your health care provider for advice before taking any medicine. Be sure to tell your health care provider immediately if you are or may be pregnant.
In babies born to mothers who have taken antiretroviral medicines comprising nucleoside and nucleotide analogues, the benefit of reduced risk of becoming infected with HIV outweighs the risk of side effects of these medicines.
If you are interested in breastfeeding your baby, you should discuss the risks and benefits with your healthcare provider.

Driving and using machines

Dizziness can occur during treatment with [HA433 trade name]. If you experience these symptoms you should avoid potentially hazardous tasks such as driving and operating machinery.

Important information about some of the ingredients of [HA433 trade name].

[HA433 trade name] contains lactose. If your health care provider has told you that your child has an intolerance to some sugars, contact your health care provider before giving your child [HA433 trade name].

[HA433 trade name] also contains **aspartame** in each tablet. Aspartame is a source of phenylalanine. It may be harmful if your child has phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

It is important to consider the contribution of ingredients from all the medicines that your child is taking.

3. How to take [HA433 trade name]

Always give your child [HA433 trade name] exactly as the health care provider told you. You should check with the health care provider if you are not sure.
The dose of [HA433 trade name] is determined on the basis of your child's body weight.

The number of tablets, by weight band, to be taken twice daily (approximately 12 hours apart) is shown in the table below:

Child's weight	**Number of tablets**	
	Morning	**Evening**
3 kg to less than 6kg	One tablet	One tablet
6 kg to less than 10 kg	One-and-a-half tablet	One-and-a-half tablet
10 kg to less than 14 kg	Two tablets	Two tablets
14 kg to less than 20 kg	Two-and-a-half tablets	Two-and-a-half tablets
20 kg to less than 25 kg	Three tablets	Three tablets

Children weighing 25 kg or more
For children weighing 25 kg or more, adolescents and adults, other products with larger amounts of the active substances are available. Please see the patient information leaflets of the respective products.

Dose adjustments
If your child's dose of [HA433 trade name] needs to be reduced, for example if he/she has kidney problems or discontinuation of therapy with one of the active substances of [HA433 trade name] is necessary, then your child's medicine may be changed to separate preparations of lamivudine, zidovudine and nevirapine, which are available as tablets/capsules and liquid formulations for oral use.

If one takes more [HA433 trade name] than one should:

If your child has accidently taken too many tablets, or if someone accidentally swallows some, there is no immediate danger. However, you should contact the health care provider or the nearest hospital emergency department for further advice. Take the tablet container with you so that you can easily describe what they have taken.

If one forgets to take [HA433 trade name]

If your child accidentally misses a dose and you notice within 6 hours after the missed dose, give the missed dose as soon as possible. Give the next dose as regularly scheduled. If you notice later than 6 hours after the missed dose, then only give the normal dose when the next dose is due. Do not give a double dose to make up for forgotten individual doses.
If your child throws up the tablet (just after taking [HA433 trade name]) he/she should take another tablet. Do not wait until your child's next dose is due.

If one stops taking [HA433 trade name]

Your child should not stop taking [HA433 trade name] without talking to his/her health care provider. Stopping [HA433 trade name] can seriously affect your child's response to future treatment. If [HA433 trade name] is stopped, speak to your child's health care provider before your child restarts taking [HA433 trade name]. Your child's health care provider may consider giving him/her the components of [HA433 trade name] separately if your child is having problems or need his/her dose adjusted.
When your child's supply of [HA433 trade name] starts to run low, get more from his/her 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 any further questions on the use of this product, ask the health care provider.
[HA433 trade name] should be given every 12 hours and it can be given with food or between meals.

Giving [HA433 trade name]
Using dry hands take the required number of tablets according to the recommended dose and place it in a drinking container such as a tumbler or a beaker. Then add the required amount of water to the container. The amount of water to be used for dispersing the dose is shown below:

Dose of [HA433 trade name] recommended for the child	**Minimum volume of drinking water to be used**
1 or 1½ tablets	10 mL (about 2 teaspoonfuls)
2 or 2½ tablets	15 mL (about 3 teaspoonfuls)
3 tablets	20 mL (about 4 teaspoonfuls)

Swirl or stir the mixture to disperse the tablets completely. You should ensure that your child drink all of the mixture. Rinse the container with more water and give your child to drink so that the whole dose is taken. The water and all the mixture should be swallowed within 10 minutes.

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 [HA433 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 [HA433 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 [HA433 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 [HA433 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 [HA433 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 [HA433 trade name]

Do not store above 30°C. Store in the original package, protected from moisture. 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 and carton after 'EXP'. The expiry date refers to the last day of that month.

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 [HA433 trade name] contains

The active substances are lamivudine, nevirapine and zidovudine.

The other ingredients are lactose monohydrate, microcrystalline cellulose, povidone K30, colloidal silicon dioxide, sodium starch glycolate, magnesium stearate, ferric oxide yellow, orange flavor, aspartame and acesulfame potassium.

What [HA433 trade name] looks like and contents of the pack

Yellow coloured, mottled, round shaped, beveled edged tablets with break-line and debossed with 'M09' on one side and plain on the other.

The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

[HA433 trade name] is stored in a white, opaque, wide-mouth HDPE bottle, with a white, opaque cap and containing a desiccant.

Pack size: 60 tablets.

Supplier

Mylan Laboratories Limited,
Plot No. 564/A/22, Road No. 92, Jubilee Hills
Hyderabad - 500096, Telangana,
India
Tel No: +91 40 39258109
Email: imtiyaz.basade@mylan.in

Manufacturers

Mylan Laboratories Limited,
F-4, F-12, Malegaon M.I.D.C,
Sinnar, Nashik District– 422113,
Maharashtra State
India.

Mylan Laboratories Limited
H-12 & H-13, M.I.D.C, Waluj
Aurangabad– 431136
Maharashtra State
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Mylan Laboratories Limited
Plot No. 11, 12 & 13
Indore Special Economic Zone, Phase – II, Sector – III,
Pithampur – 454775,
Dist- Dhar, M.P.
India.

For any information about this medicine, contact the supplier:

This leaflet was last revised in February 2020

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