PACKAGE LEAFLET: INFORMATION FOR THE USER

DUOVIR N *

(Lamivudine/Zidovudine /Nevirapine 150/ 300/200 mg)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, health care provider or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What DUOVIR N is and what it is used for
2. Before you take DUOVIR N
3. How to take DUOVIR N
4. Possible side effects
5. How to store DUOVIR N
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1. WHAT DUOVIR N IS AND WHAT IT IS USED FOR

DUOVIR N 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.

DUOVIR N is used as antiretroviral combination therapy for the treatment of HIV infection. The three medicines contained in DUOVIR N 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 DUOVIR N is the same as that recommended for the medicines when used separately. Treatment with DUOVIR N will only be instituted by your doctor or health care provider, when you have been shown to be stable on the three individual compounds. DUOVIR N 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 DUOVIR N varies between patients. Your doctor or health care provider will be monitoring the effectiveness of your treatment.

DUOVIR N 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 DUOVIR N 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.

2. BEFORE YOU TAKE DUOVIR N

Do not take DUOVIR N:

- if you are hypersensitive (allergic) to lamivudine, zidovudine, nevirapine or any of the other ingredients of DUOVIR N (see section 6, What DUOVIR N 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,

* Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

- if you previously experienced liver inflammation, severe skin rash or liver injury while on treatment with nevirapine-containing products.
- Patients taking DUOVIR N must not take products containing rifampicin or St. John's wort *(Hypericum perforatum*) as this may stop DUOVIR N from working properly.

Take special care with DUOVIR N:

Before using DUOVIR N, you should have told your doctor or 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 doctor or health care provider knows about all your symptoms even when you think they are not related to HIV infection. Your doctor or health care provider may decide to prescribe lamivudine, zidovudine and/or nevirapine as separate medicines instead of DUOVIR N.

Liver disease

During the first 10 to 12 weeks of treatment with DUOVIR N your doctor will closely monitor you for the occurrence of severe and life-threatening skin reactions and serious hepatic injuries.

As DUOVIR N may cause changes in liver function, your doctor will monitor the function of your liver by blood tests before and at regular intervals during treatment with DUOVIR N. 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 any of these risk factors applies to you, your doctor 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 the benefit outweighs 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 DUOVIR N and must contact your doctor immediately.

If you have a chronic hepatitis B infection, you should not stop your treatment without instructions from your doctor or 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 DUOVIR N, regular blood tests will be arranged to check whether there is a problem.

Skin reactions

DUOVIR N 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 DUOVIR N right away and and must contact your doctor immediately.

If you develop severe liver, skin or allergic reactions while taking DUOVIR N, never take DUOVIR N or any other nevirapine-containing product again without asking your doctor or 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 3). While you are being treated with DUOVIR N your doctor or 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 doctor or 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 doctor or health care provider.

You will need to take DUOVIR N 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 doctor or health care provider. Do not stop taking your medicine without first talking to your doctor or health care provider.

Taking other medicines

Please tell your doctor, health care provider or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of DUOVIR N, or DUOVIR N may affect their action.

DUOVIR N must not be taken with rifampicin.
DUOVIR N must not be taken with herbal preparations containing St. John’s Wort.

DUOVIR N 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).

DUOVIR N may also interact with the following medicines and may make any side effects worse or may impact on the either 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 DUOVIR N.
- fluconazole (antifungal medicine),
- clarithromycin, rifabutin (antibiotics),
- artemisinines, amodiaquine/artesunate, quinine, lumefantrine, halofantrine, atovaquone (antimalarials),
- phenytoin, valproic acid (anticonvulsants),
- warfarin (medicine for prophylaxis of blot clots),
- doxorubicin (anti-cancer medicine).

Taking DUOVIR N with food and drink

DUOVIR N 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 doctor or health care provider to discuss the potential benefits and risks of your antiretroviral therapy to you and your child.
If you have taken DUOVIR N during your pregnancy, your doctor or 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 want to breastfeed your baby you should ask your doctor or healthcare provider for advice on the risks and benefits. Treatment of mother and/or child with medicines may be needed. Generally it is recommended that HIV-infected women should not breast-feed their infants because of the possibility that the baby may be infected with HIV through the breast milk.

Driving and using machines

DUOVIR N may cause side effects such as drowsiness or headache, that can impair your ability to drive and to use machines.

3. HOW TO TAKE DUOVIR N

Always take DUOVIR N exactly as your doctor or health care provider told you. You should check with your doctor, health care provider or pharmacist if you are not sure.

The recommended dose of DUOVIR N in adults and children with a body weight of 25 kg or more is one tablet twice daily.

Children:
DUOVIR N is not indicated for children weighing less than 25 kg, since appropriate dose reductions cannot be made.

Dose adjustments:
If your dose of DUOVIR N needs to be reduced, for example if you have kidney problems or discontinuation of therapy with one of the active substances of DUOVIR N 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 DUOVIR N 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 doctor, health care provider or the nearest hospital emergency department for further advice.

If you forget to take DUOVIR N

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 DUOVIR N

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 doctor or health care provider tells you to.

If you have any further questions on the use of this product, ask your doctor or health care provider or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, DUOVIR N 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 DUOVIR N, 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 doctor or health care provider of any change in your health.

The major side effects of DUOVIR N are severe and life-threatening cutaneous reactions and serious hepatic injuries. These occur mainly in the first 10 to 12 weeks of treatment with DUOVIR N. This is therefore an important period which requires close surveillance (see “take special care with DUOVIR N).

The most *commonly* reported (greater than 1 in every 100 patients treated) side effects are fatigue, headache, nausea, vomiting, stomach pain, diarrhoea, fever, rash (red, raised or itchy), increase in certain liver enzymes, joint pain, 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 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, Before you take DUOVIR N).

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, Before you take DUOVIR N).

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 other 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 “Take special care with DUOVIR N”).

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 “Take special care with DUOVIR N”).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or health care provider or pharmacist as soon as possible.

5. HOW TO STORE DUOVIR N

Keep out of the reach and sight of children.

Do not store above 30 °C.

Do not use DUOVIR N after the expiry date which is stated on the label.
The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What DUOVIR N contains

The active ingredients are lamivudine, zidovudine and nevirapine.

The other ingredients are microcrystalline cellulose, sodium starch glycolate, corn starch, povidone, magnesium stearate, Opadry 04F58804 white (Hypromellose, titanium dioxide and PEG 6000).

What DUOVIR N looks like and contents of the pack

White capsule shaped, biconvex film coated tablets debossed with “LZN” on one side and plain on the other side.

The tablets should not be divided.

Tablets are available in HDPE bottle of 30 and 60 tablets.

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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) web site: http://www.who.int/prequal/ .