Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
The medicine is dispensed according to a physician's prescription only

COMBIVIR

150 mg/300 mg film coated tablets
Each tablet contains: lamivudine 150 mg and zidovudine 300 mg.
List of the additional ingredients detailed in section 6.

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the physician or the pharmacist.

This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them even if it seems to you that their illness is similar.

1. What is the medicine intended for?

Combivir is indicated in anti viral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.
Therapeutic group: Combivir contains two active ingredients that are used to treat HIV infection: lamivudine and zidovudine. Both of these belong to a group of anti-retroviral medicines called: nucleoside analogue reverse transcriptase inhibitors (NRTIs).
Combivir does not completely cure HIV infection. It reduces the amount of virus in your body, and keeps it at a low level. It also increases the CD4 cell count in your blood. CD4 cells are a type of white blood cells that are important in helping your body to fight infection.
Not everyone responds to treatment with Combivir in the same way. Your physician will monitor the effectiveness of your treatment.

2. Before using the medicine

Do not use the medicine if:
- You are sensitive (allergic) to the active ingredients or to any of the additional ingredients contained in the medicine, see section 6.
- You have **a very low red blood cell count** *(anaemia)* or **a very low white blood cell count** *(neutropenia)*.

→ **Talk with your physician** if you think any of these apply to you.

Special warnings regarding the use of this medicine
Some people taking Combivir or other combination treatments for HIV are more at risk of having serious side effects. You need to be aware of the extra risks:
- if you have ever had **liver disease**, including hepatitis B or C (if you have hepatitis B infection, do not stop treatment with Combivir without your physician's advice as the hepatitis may come back)
- if you have **kidney disease**
- if you are seriously **overweight** (especially if you are a woman)

→ **Talk to your physician if any of these apply to you.** Your physician will decide if the active substances are suitable for you. You may need extra check-ups, including blood tests, while you are taking your medicine. For more information, see section 4.

Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Combivir.
→ **Read the information "Other possible side effects of combination therapy for HIV" in section 4 of this leaflet.**

Protect other people
HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV when taking this medicine, although the risk is lowered by effective antiretroviral therapy.
Discuss with your doctor the precautions needed to avoid infecting other people.

Other medicines and Combivir
If you are taking or have recently taken other medicines including non-prescription medicines and food supplements, tell the physician or the pharmacist.
Remember to tell your physician or pharmacist if you begin taking a new medicine while you are taking Combivir.

Do not use these medicines with Combivir:
- other medicinal products containing lamivudine, to treat **HIV infection or hepatitis B infection**
- emtricitabine, to treat **HIV infection**
- stavudine, to treat **HIV infection**
- ribavirin or injections of ganciclovir, to treat **viral infections**
- high doses of **co-trimoxazole**, an antibiotic
- cladribine, used to treat **hairy cell leukaemia**

→ **Talk to your physician** if you are being treated with any of these.

Some medicines can make it more likely that you'll have side effects, or make side effects worse.
These include:
- sodium valproate, to treat **epilepsy**
- interferon, to treat **viral infections**
- pyrimethamine, to treat **malaria** and other parasitic infections
- dapsone, to prevent **pneumonia** and treat skin infections
- fluconazole or flucytosine, to treat **fungal infections** such as ***Candida***
- pentamidine or atovaquone, to treat parasitic infections such as *Pneumocystis jirovecii* pneumonia (often referred to as PCP)
- amphotericin or co-trimoxazole, to treat **fungal and bacterial infections**
- probenecid, to treat **gout** and similar conditions, and given with some antibiotics to make them more effective
- **methadone**, used as a **heroin substitute**
- vincristine, vinblastine or doxorubicin, to treat **cancer**

→ **Tell your physician** if you are taking any of these.

Some medicines interact with Combivir
These include:
- **clarithromycin**, an antibiotic

→ If you are taking clarithromycin, take your dose at least 2 hours before or after you take Combivir.
- **phenytoin**, for treating **epilepsy**

→ **Tell your physician** if you are taking phenytoin. Your physician may need to monitor your condition while you are taking Combivir.
- medicines (usually liquids) containing **sorbitol and other sugar alcohols** (such as xylitol, mannitol, lactitol or maltitol), if taken regularly.

→ **Tell your physician or pharmacist** if you are taking any of these.

Pregnancy, breast-feeding and fertility
Pregnancy
If you are pregnant, if you become pregnant or if you are planning to become pregnant, consult the physician about the risks and benefits to you and your baby of taking Combivir.
Combivir and similar medicines may cause side effects in unborn babies. If you have taken Combivir during your pregnancy, your physician may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

Breast-feeding
Women who are HIV-positive must not breastfeed, because HIV infection can be passed on to the baby in breast milk.
A small amount of the ingredients in Combivir can also pass into your breast-milk.
If you're breast-feeding, or thinking about breast-feeding:
→ **Talk to your physician immediately.**

Driving and using machines
Combivir can make you dizzy and have other side effects that make you less alert.
→ **Do not drive or operate machines** unless you are feeling well.

3. How should you use the medicine?

Always use according to the physician's instructions.
You should check with the physician or the pharmacist if you are unsure.
The dosage and treatment will be determined only by the physician.
Swallow Combivir tablets with some water. Combivir can be taken with or without food.
If you cannot swallow the tablets whole, you may crush them, combine them with a small amount of food or drink and take all the dose immediately.
It is allowed to crush/halve the tablets. There is no information regarding chewing.

Stay in regular contact with your physician
Combivir helps to control your condition. You need to keep taking it every day to stop your illness getting worse. You may still develop other infections and illnesses linked to HIV infection.
→ **Keep in touch with your physician, and do not stop taking Combivir** without your physician's advice.

The usual dosage is generally:
Adults and adolescents weighing 30 kg or more
The usual dose is generally one tablet twice a day.
Take the tablets at regular times, leaving approximately 12 hours between each tablet.
Children who weigh between 21 and 30 kg
The usual starting dose of Combivir is one half tablet (½) taken in the morning and one whole tablet taken in the evening.
Children who weigh between 14 and 21 kg
The usual starting dose of Combivir is one half tablet (½) taken in the morning and one half tablet (½) taken in the evening.
For children who weigh less than 14 kg, lamivudine and zidovudine (the ingredients of Combivir) should be taken separately.
Do not exceed the recommended dose

If you accidentally have taken a higher dosage or if a child has accidentally swallowed the medicine, refer immediately to a physician or to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take this medicine at the scheduled time, take it as soon as you remember. Then continue your treatment as usual. Do not take a double dose to make up for a forgotten dose.

Persist with the treatment as recommended by the physician.

Even if there is an improvement in your health, do not stop the treatment with the medicine without consulting the physician or the pharmacist.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.

If you have any other questions regarding the use of the medicine, consult the physician or the pharmacist.

4. 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 health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your physician will test these changes.

Treatment with Combivir often causes a loss of fat from legs, arms and face (lipoatrophy). This loss of body fat has been shown to be not fully reversible after discontinuation of zidovudine. Your physician should monitor for signs of lipoatrophy. Tell your physician if you notice any loss of fat from your legs, arms, and face. When these signs occur, treatment with Combivir should be stopped and your HIV treatment changed.

As with any medicine, use of Combivir may cause side effects in some of the users. Do not be alarmed by reading the list of side effects. You may not experience any of them.

When you are being treated for HIV infection, it can be hard to tell whether a symptom is a side effect of Combivir or other medicines you are taking, or an effect of the HIV disease itself. **So it is very important to talk to your physician about any changes in your health.**
As well as the side effects listed below for Combivir, other conditions can develop during combination therapy for HIV infection.
→ It is important to read the information later in this section under "Other possible side effects of combination therapy for HIV".

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- nausea (*feeling sick*).

Common side effects
These may affect **up to 1 in 10** people:
- vomiting (*being sick*)
- diarrhoea
- stomach pains
- loss of appetite
- feeling dizzy
- tiredness, lack of energy
- fever (*high temperature*)
- general feeling of being unwell
- difficulty in sleeping (*insomnia*)
- muscle pain and discomfort
- joint pain
- cough
- irritated or runny nose
- skin rash
- hair loss (*alopecia*).

Common side effects that might show up in blood tests are:
- a low red blood cell count (*anaemia*) or low white blood cell count (*neutropenia or leucopenia*)
- an increase in the level of liver enzymes
- an increased amount in the blood of *bilirubin* (a substance produced in the liver) which may cause yellowing of the skin.

Uncommon side effects
These may affect **up to 1 in 100** people:
- shortness of breath
- wind (*flatulence*)
- itching
- muscle weakness.

An uncommon side effect that may show up in blood tests is:
- a decrease in the number of cells involved in blood clotting (*thrombocytopenia*) or decrease in all kinds of blood cells (*pancytopenia*).

Rare side effects
These may affect **up to 1 in 1,000** people:
- serious allergic reaction causing swelling of the face, tongue or throat which may cause difficulty in swallowing or breathing
- liver disorders, such as jaundice, enlarged liver or fatty liver, inflammation (*hepatitis*)
- lactic acidosis (excess lactic acid in the blood; see later in this section, "Other possible side effects of combination therapy for HIV")
- inflammation of the pancreas (*pancreatitis*)
- chest pain, disease of the heart muscle (*cardiomyopathy*)
- fits (*convulsions*)
- feeling depressed or anxious, not being able to concentrate, feeling drowsy
- indigestion, taste disturbance
- changes in the colour of your nails, your skin or the skin inside your mouth
- a flu-like feeling – chills and sweating
- tingly feelings in the skin (pins and needles)
- sensation of weakness in the limbs
- breakdown of muscle tissue
- numbness
- passing urine more often
- enlarged breasts in men.

Rare side effects that may show up in blood tests are:
- an increase in an enzyme called amylase
- a failure of the bone marrow to produce new red blood cells (*pure red cell aplasia*).

Very rare side effects
These may affect **up to 1 in 10,000** people:
A very rare side effect that may show up in blood tests is:
- a failure of the bone marrow to produce new red or white blood cells (*aplastic anaemia*).

If any of the side effects get worse, or when you suffer from a side effect not mentioned in the leaflet, you should consult the physician or pharmacist.

Other possible side effects of combination therapy for HIV
Combination therapy such as Combivir may cause other medical conditions to develop during HIV treatment.

Old infections may flare up
People with advanced HIV infection (AIDS) have weak immune system, and are more likely to develop serious infections (opportunistic infections). When these people start treatment, they may find that old, hidden infections flare up, causing signs and symptoms of infection. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections.
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 physician immediately to seek necessary treatment.
If you get any symptoms of infection while you are taking Combivir:
→ **Talk to your physician immediately.** Do not take other medicines for the infection without your physician's advice.

Lactic acidosis is a rare but serious side effect
Some people taking Combivir develop a condition called lactic acidosis, together with an enlarged liver.
Lactic acidosis is caused by a build-up of lactic acid in the body. It is rare; if it happens, it usually develops after a few months of treatment. It can be life-threatening, causing failure of internal organs. Lactic acidosis is more likely to develop in people who have liver disease, or in obese (very overweight) people, especially women.

Signs of lactic acidosis include:
- deep, rapid, difficult breathing
- drowsiness
- numbness or weakness in the limbs
- feeling sick (nausea), being sick (vomiting)
- stomach pain.

During your treatment, your physician will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above or any other symptoms that worry you:
→ **Talk to your physician as soon as possible.**

You may have problems with your bones
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
- they are also taking anti-inflammatory medicines called corticosteroids
- they drink alcohol
- their immune system is very weak
- they are overweight.

Signs of osteonecrosis include:
- stiffness in the joints
- aches and pains (especially in the hip, knee or shoulder)
- difficulty moving.

If you notice any of these symptoms:
→ **Talk to your physician.**

Other effects may show up in blood tests
Combination therapy for HIV can also cause:
- increased levels of lactic acid in the blood, which on rare occasions can lead to lactic acidosis.

If any of the side effects get worse, or when you suffer from a side effect not mentioned in the leaflet, you should consult the physician.

Adverse events can be reported to the Ministry of Health by clicking the link "Report Side Effects of Drug Treatment" that is located on the Ministry of Health home page (www.health.gov.il), which refers to on-line form for adverse events reporting, or by entering the link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without an explicit instruction from the physician.
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
- Bottle pack: Use within 3 months after opening.
- Store below 30°C.

6. Additional information

- In addition to the active ingredients the medicine also contains – microcrystalline cellulose, sodium starch glycollate, magnesium stearate, colloidal silicon dioxide, hydroxypropyl methylcellulose, titanium dioxide (E171), polyethylene glycol 400, polysorbate 80
- What does the medicine look like and what is the content of the package-
  Combivir film-coated tablets are provided in a carton containing blister packs or bottle with a child-resistant closure. Each pack type contains 60 film-coated tablets. They are white to off-white, capsule-shaped scored tablets marked with the code GXFC3 on both sides.
  Not all packs may be marketed.
- License Holder: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva
- Manufacturer: GlaxoSmithKline Pharmaceuticals S.A., Poznan, Poland
- The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by the Ministry of Health in November 2016, and updated in March 2018, in accordance with Ministry of Health guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 110-32-29328

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