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

ZIAGEN TABLETS, 300 mg

Film-coated tablets.

Each tablet contains Abacavir (as sulfate) 300 mg.

A list of the additional ingredients is detailed in section 6.

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the physician or 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.

IMPORTANT - Hypersensitivity reactions

Ziagen contains abacavir (which is also an active substance in medicines such as **Kivexa, Triumeq and Trizivir**). Some people who take abacavir may develop a **hypersensitivity reaction** (a serious allergic reaction), which can be life-threatening if they continue to take abacavir-containing preparations.
You must carefully read all the information under 'Hypersensitivity reactions' in the panel in section 4.

The Ziagen pack includes an **Alert Card,** to remind you and the medical staff about abacavir hypersensitivity .
Detach this card and keep it with you at all times.
This card contains important safety information that you must know and abide by before starting treatment and during the course of treatment with Ziagen. Read the Alert Card and patient leaflet before starting to use the preparation.

1. What is the medicine intended for?

Ziagen is used to treat HIV (human immunodeficiency syndrome) infection.

Therapeutic group: Ziagen contains the active ingredient abacavir. Abacavir belongs to a group of anti-retroviral medicines called *nucleoside analogue reverse transcriptase inhibitors (NRTIs).*

Ziagen 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 cell that are important in helping your body fight infection.

Not everyone responds to treatment with Ziagen 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 abacavir (or any other medicine containing abacavir such as **Trizivir, Triumeq** or **Kivexa**) or to any of the additional ingredients contained in the medicine (detailed in section 6).
  Carefully read all the information about hypersensitivity reactions in section 4.

Check with your physician if you think this applies to you.

Special warnings regarding the use of the medicine
Some people taking Ziagen for HIV are more at risk of serious side effects. You need to be especially aware of the extra risks:
- if you have **moderate or severe liver disease**
- if you have ever had a **liver disease** in the past, including hepatitis B or C
- if you are seriously **overweight** (especially if you are a woman)
- if you have a **severe kidney disease.**

Refer to your physician if any of these apply to you. You may need extra check-ups, including blood tests, while you are taking your medicine. **See section 4 for more information.**

Abacavir hypersensitivity reactions
Even patients who do not have the HLA-B*5701 gene may still develop a **hypersensitivity reaction** (a serious allergic reaction).

Carefully read all the information about hypersensitivity reactions in section 4 of this leaflet.

Risk of heart attack
It cannot be excluded that abacavir may increase the risk of having a heart attack.
Tell your physician if you have heart problems, if you smoke, or have other illnesses that may increase your risk of heart disease such as high blood pressure, or diabetes. Do not stop taking Ziagen unless your physician advises you to do so.

Look out for important symptoms
Some people taking medicines for HIV infection develop other medical conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking Ziagen.
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 carrying the infection, or by transfer of infected blood (for example, by sharing injection needles). You can still pass on HIV infection when taking this medicine, although the risk is lowered by effective anti-retroviral therapy. Discuss with your physician the precautions needed to avoid infecting other people.

Other medicines and Ziagen
If you are taking, or have recently taken, other medicines, including

non-prescription medicines and food supplements, tell the physician or pharmacist. Remember to tell your physician or pharmacist if you begin taking a new medicine while you are taking Ziagen.
There are medicines that interact with Ziagen
These include:
- **phenytoin,** for treating **epilepsy.**
  Tell your physician if you are taking phenytoin. Your physician may need to monitor your condition while you are taking Ziagen.
- **methadone** used as a **heroin substitute.** Abacavir increases the rate at which methadone is removed from the body. If you are taking methadone, you will be checked for withdrawal symptoms. Your methadone dose may need to be changed.
  Tell your physician if you are taking methadone.

Pregnancy, breast-feeding and fertility

Pregnancy
Ziagen is not recommended for use during pregnancy. Ziagen and similar medicines may cause side effects in unborn babies. If you have taken Ziagen 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 breast-feed, because HIV infection can be passed on to the baby in breast milk. A small amount of the active substance in Ziagen can also pass into your breast milk.
If you are breast-feeding, or thinking about breast-feeding: **Refer to the physician immediately.**

Driving and operating machines
Do not drive or operate machines unless you are feeling well.

3. How should you use the medicine?

Always use the preparation according to the physician's instructions. You should check with the physician or the pharmacist if you are unsure about the preparation dosage and treatment regimen.

The dosage and treatment regimen will be determined by the physician only.

Swallow Ziagen tablets with some water. Ziagen can be taken with or without food.

If you cannot swallow the tablet(s), you may crush and mix them with a small amount of food or drink, and take the entire dose immediately .

The tablets may be crushed, halved or chewed.

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

The usual dosage is generally:

Adults, adolescents and children weighing at least 25 kg

The usual dosage of Ziagen is 600 mg a day. This can be taken either as one 300 mg tablet, twice a day or as two 300 mg tablets, once a day.

Children from one year of age weighing less than 25 kg

The dosage given depends on the body weight of your child. The recommended dosage is:

- Children weighing at least 20 kg and less than 25 kg: The usual dosage of Ziagen is 450 mg per day. This can be given as 150 mg (half a tablet) in the morning, and 300 mg (one whole tablet) in the evening, or 450 mg (one and a half tablets) once a day, as advised by your physician.

- Children weighing at least 14 kg and less than 20 kg: The usual dosage of Ziagen is 300 mg per day given as 150 mg (half a tablet) twice a day, or 300 mg (one whole tablet) once a day, as advised by your physician.

The tablet can be divided into equal doses.

An oral solution (20 mg abacavir/ml) is also available for the treatment of children over three months of age and weighing less than 14 kg, for people who need a lower than usual dosage, or who cannot take tablets.
Do not exceed the recommended dose.

If you have accidentally 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.

Adhere to 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.

It is important to take Ziagen regularly, because if you take the medicine at irregular intervals, you are more likely to experience a hypersensitivity reaction.

If you stop taking the medicine
If you have stopped taking Ziagen for any reason - especially because you think you are having side effects, or because you have another illness: **Refer to your physician before you start taking it again.** Your physician will check whether your symptoms were related to a hypersensitivity reaction. If the physician thinks that they may have been related, **you will be instructed never again to take Ziagen, or any other medicine containing abacavir (e.g., Trizivir, Triumeq or Kivexa).** It is important that you follow this guideline.

If your physician advises that you can start taking Ziagen again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

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

If you have further 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 restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your physician will test for these changes.

As with any medicine, use of Ziagen tablets may cause side effects in some of the users. Do not be alarmed by reading the list of side effects. You may not suffer from 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 Ziagen or other medicines you are taking, or an effect of the HIV disease itself. **Therefore, it is very important to talk to your physician about any changes in your health.**

Even patients who do not have the HLA-B*5701 gene may still develop a **hypersensitivity reaction** (a serious allergic reaction), described in this leaflet in the panel headed 'Hypersensitivity reactions'.

It is very important that you read and understand the information about this serious reaction.

In addition to the side effects listed below for Ziagen, other medical conditions can develop during combination therapy for HIV.
It is important to read the information that appears later in this section under 'Other possible side effects of combination therapy for HIV'.

Hypersensitivity reactions

Ziagen contains **abacavir** (which is also an active substance **in Trizivir, Triumeq and Kivexa**). Abacavir can cause a serious allergic reaction known as a hypersensitivity reaction.

These hypersensitivity reactions have been seen more frequently in people taking medicines that contain abacavir.

Who develops these reactions?
Anyone taking Ziagen could develop a hypersensitivity reaction to abacavir, which could be life-threatening if they continue to take Ziagen.

You are more likely to develop such a reaction if you have the **HLA-B*5701** gene (but you can develop a reaction even if you do not have this gene). You should have been tested for this gene before Ziagen was prescribed for you. **If you know you have this gene, tell your physician before you take Ziagen.**

About 3 to 4 in every 100 patients treated with abacavir in a clinical trial, who did not have the HLA-B*5701 gene, developed a hypersensitivity reaction.

What are the symptoms?

The most common symptoms are:
˚ **fever and skin rash.**

Other common symptoms are:
˚ nausea, vomiting, diarrhoea, abdominal pain, severe tiredness.

Other symptoms include:
Pains in the joints or muscles, swelling of the neck, shortness of breath, sore throat, cough, transient headache, inflammation of the eye *(conjunctivitis)*, mouth ulcers, low blood pressure, tingling or numbness of the hands or feet.

When do these symptoms occur?
Hypersensitivity reactions can start at any time during treatment with Ziagen, but are more likely during the first 6 weeks of treatment.

If you are caring for a child who is being treated with Ziagen, it is important that you understand the information about this hypersensitivity reaction. If your child develops the symptoms described below it is essential that you follow the instructions given.

Contact your physician immediately:
1. if you or your child develops a skin rash, OR
2. if you or your child develops symptoms from at least 2 of the following groups:
˚ fever
˚ shortness of breath, sore throat or cough
˚ nausea or vomiting, diarrhoea or abdominal pain
˚ severe tiredness or pain, or generally feeling ill.
Your physician may advise you to stop taking Ziagen.

If you have stopped taking Ziagen

If you have stopped taking Ziagen because of a hypersensitivity reaction, **you must NEVER AGAIN take Ziagen, or any other medicine containing abacavir (e.g., Trizivir, Triumeq or Kivexa).** If you take them, your blood pressure could fall dangerously low within hours, which could result in death.

If you have stopped taking Ziagen for any reason - especially because you think you are having side effects, or because you have another illness:
Talk to your physician before you start taking it again. Your physician will check whether your symptoms were related to a hypersensitivity reaction. If the physician thinks that they may have been related, **you will then be instructed never again to take Ziagen, or any other medicine containing abacavir (e.g., Trizivir, Triumeq or Kivexa).** It is important that you follow this guideline.

Occasionally, hypersensitivity reactions have developed in people who started taking abacavir-containing preparations again, but who had only one symptom on the Alert Card before they stopped taking them.

Very rarely, patients who have taken medicines containing abacavir in the past, and did not have any symptoms of hypersensitivity, have developed a hypersensitivity reaction when they started taking these medicines again.

If your physician advises that you can start taking Ziagen again, you may be asked to take your first doses in a place where you will have ready access to medical care if you need it.

If you are hypersensitive to Ziagen, return all your unused Ziagen tablets for safe disposal. Ask your physician or pharmacist for advice.

The Ziagen pack includes an **Alert Card,** to remind you and the medical staff about hypersensitivity reactions. **Detach this card and keep it with you at all times.**

Common side effects
(These may occur in **up to 1 in 10** people):
° hypersensitivity reaction
° nausea
° headache
° vomiting
° diarrhoea
° loss of appetite
° tiredness, lack of energy
° fever
° skin rash.

Rare side effects
(These may occur in **up to 1 in 1,000** people):
° inflammation of the pancreas *(pancreatitis)*.

Very rare side effects
(These may occur in **up to 1 in 10,000** people):
° skin rash, which may form blisters and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) *(erythema multiforme)*
° a widespread rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals *(Stevens–Johnson syndrome)*, and a more severe form causing skin peeling in more than 30% of the body surface *(toxic epidermal necrolysis)*
° lactic acidosis (excess lactic acid in the blood)
If you notice any of these symptoms contact a physician urgently.

Other possible side effects of combination therapy for HIV

Combination therapy including Ziagen may cause other medical conditions to develop during HIV treatment.

Symptoms of infection and inflammation

Old infections may flare up

People with advanced HIV infection (AIDS) have a 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 inflammation. These symptoms are probably caused by the body's immune system becoming stronger, so that the body starts to fight these infections. 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 suffer from any symptoms of infection while you are taking Ziagen: **Tell your physician immediately.** Do not take other medicines against the infection without your physician's advice.

You may have problems with your bones

Some people receiving combination therapy for HIV develop a condition called *osteonecrosis* (necrosis of the bone). 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
˚ pains (especially in the hip, knee or shoulder)
˚ difficulty moving.
If you notice any of these symptoms: **Tell your physician.**

If a side effect occurs, if one of the side effects worsens or when you suffer from a side effect not mentioned in the leaflet, consult the physician.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, 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 sight and reach 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.

˚ Do not store above 30°C.

6. Additional information

˚ In addition to the active ingredient the medicine also contains - microcrystalline cellulose, sodium starch glycollate (Type A), magnesium stearate, colloidal anhydrous silica, methylhydroxypropylcellulose, titanium dioxide (E171), triacetin, iron oxide yellow (E172) and polysorbate 80.

˚ What the medicine looks like and the contents of the package - Ziagen film-coated tablets are engraved with 'GX 623' on both sides. They are scored, yellow, capsule-shaped tablets and are provided in blister packs containing 60 tablets.

˚ License Holder: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

˚ Manufacturer: GlaxoSmithKline Pharmaceuticals S.A., Poznan, Poland.

˚ This leaflet was checked and approved by the Ministry of Health in January 2019.

˚ Registration number of the medicine in the National Drug Registry of the Ministry of Health: 112-97-29542.

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