PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a physician's prescription only

Retrovir IV for Infusion

Solution for Intravenous Infusion

Each vial contains:

zidovudine 200 mg/20 ml

Each 1 ml of solution contains 10 mg zidovudine.

For a list of inactive and allergenic ingredients in the preparation, see section 2 – "Important information about some of the ingredients of the medicine" and section 6 – "Further information".

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 you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Retrovir IV for infusion is indicated for the short term management of serious manifestations of Human immunodeficiency Virus (HIV) infection in patients with Acquired Immuno Deficiency Syndrome (AIDS) or AIDS who are unable to take Retrovir oral formulations.

Retrovir chemoprophylaxis, is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) for prevention of maternal-foetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants. Retrovir IV should only be used when oral treatment is not possible (except during labour and delivery).

Therapeutic group:

The active ingredient in Retrovir is zidovudine. Retrovir belongs to a group of anti-retroviral medicines called *nucleoside analogue reverse transcriptase inhibitors (NRTIs).*

Retrovir does not get rid of HIV infection; it reduces the amount of virus in your body, and keeps it at a low level. Retrovir 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.

Retrovir is used, in combination with other medicines (combination therapy), to treat adults and children. To control HIV infection and to stop the illness getting worse, you must make sure to take all your medicines.

If you are pregnant, your physician may want you to take Retrovir, to prevent you passing the HIV virus on to your unborn baby. After the birth, your baby may be given Retrovir to prevent it from getting infected with the HIV virus.

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).

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are **sensitive** (allergic) to the active ingredient (zidovudine) or any of the additional ingredients contained in the medicine (as listed in section 6)
- **You have a very low white blood cell count** (*neutropenia*) **or a very low red blood cell count** (*anaemia*).

Retrovir for newborn babies:

Retrovir must not be given to some newborn babies suffering from liver problems, including:

- Some cases of *hyperbilirubinemia* (increased amounts in the blood of a substance called *bilirubin* which may make the skin appear yellow)
- Other problems which cause high levels of liver enzymes in the blood.

Special warnings regarding use of the medicine

Some people taking Retrovir or combination therapy for HIV are at higher risk of 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 are seriously overweight** (especially if you are a woman).

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

Look out for important symptoms

Some people taking medicines for HIV infection develop other conditions, which may be serious. You need to know about important signs and symptoms to look out for while you are taking Retrovir.

Please read the information in section 4 of this leaflet. If you have any questions about this information or the advice given:

→ **Consult with the physician.**

Drug interactions

If you are taking, or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the physician or pharmacist.

Do not take these medicines with Retrovir:

- **Stavudine,** used to treat **HIV infection**
- **Ribavirin** or injections of ganciclovir to treat **viral infections**
- **Rifampicin,** which is an **antibiotic.**

Some medicines may make it more likely that you will have side effects, or make side effects worse.

These include:

- **Sodium valproate,** used to treat **epilepsy**
- **Aciclovir, ganciclovir or interferon,** used to treat **viral infections**
- **Pyrimethamine,** used to treat **malaria** and other parasitic infections
- **Dapsone,** used to prevent **pneumonia** and treat **skin infections**
- **Fluconazole** or **flucytosine,** used to treat **fungal infections,** such as **Candida**
- **Pentamidine** or **atovaquone,** used to treat parasitic infections, such as **PCP**
- **Amphotericin** or **co-trimoxazole,** used to treat **fungal and bacterial infections**
- **Probenecid,** used 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,** used to treat **cancer.**

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

A medicine that interacts with Retrovir

- **Phenytoin,** used to treat **epilepsy.**

→ **Tell your physician** if you are taking phenytoin. Your physician may need to monitor you while you are taking Retrovir.

Pregnancy and breastfeeding

Pregnancy

If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant:

→ **Consult with the physician** about the risks and benefits of taking Retrovir.

If pregnant women who have HIV take Retrovir, they are less likely to pass the HIV infection on to their unborn baby.

Retrovir and similar medicines may cause side effects in unborn babies. If you have taken Retrovir during 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.

Breastfeeding

Breastfeeding is **not recommended** in women living with HIV, because the HIV infection may be passed on to the baby in breast milk.

A small amount of the ingredients in Retrovir can also pass into your breast milk.

If you are breastfeeding, or thinking about breastfeeding you should **consult with the physician as soon as possible.**

Driving and operating machinery

Retrovir may make you dizzy and have other side effects that make you less alert.

→ **Do not drive or operate machinery** unless you are feeling well.

You will need regular blood tests

While you are taking Retrovir, the physician will arrange regular blood tests to check for side effects. For more information about these side effects, see section 4 of this leaflet.

Stay in regular contact with your physician

Retrovir helps to control your condition, but it is not a cure for HIV infection. 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 the physician, and do not stop taking Retrovir** without the physician's advice.

Important information about some of the ingredients of the medicine

Retrovir contains sodium

This medicine contains less than 1 mmol **sodium** (23 mg) per dosage unit; that is to say essentially 'sodium-free'.

Vials of Retrovir for Intravenous Infusion contain latex

The rubber stopper of the vials contains latex.

→ **Tell the physician if you are allergic to latex.**

3. HOW SHOULD YOU USE THE MEDICINE?

The physician will give you the medicine by infusing it into a vein (a drip). The medicine is diluted before use and is given slowly over a one-hour period. The medicine is usually only given for short periods of time (up to 2 weeks) while you or your child are unable to take Retrovir by mouth.

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

The usual dosage is generally:

Adults and adolescents over 12 years old:

The dosage of Retrovir you receive will depend on your bodyweight. The usual dosage is 1 mg or 2 mg for each kg of bodyweight every four hours.

Children:

Your physician will decide on the correct dosage of Retrovir for your child, depending on the size of the child.

Pregnancy, childbirth and newborn babies:

You do not normally need to take Retrovir during the first 14 weeks of pregnancy. After week 14, the usual dose is 500 mg given as 100 mg five times per day taken by mouth each day until you start to go into labour. During labour and birth, your physician may give you injections of Retrovir, until your baby's umbilical cord has been clamped. Your newborn baby may also be given Retrovir to help prevent it from getting infected with HIV.

People with kidney or liver problems:

If you have severe kidney or liver problems, you may be given a lower dose of Retrovir, depending on how well your kidneys or liver are working.

→ **Ask the physician or pharmacist for advice.**

Adhere to the treatment regimen as recommended by the physician. Do not exceed the recommended dose.

If you have further questions regarding use of the medicine, consult the physician or 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 lifestyle, and in the case of blood lipids, sometimes to the HIV medicines themselves. Your physician will test for these changes.

Treatment with zidovudine (Retrovir) 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, Retrovir should be stopped and your HIV treatment changed.

As with any medicine, use of Retrovir may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Some side effects may show up in your blood tests, and may not appear until 4 to 6 weeks after you start treatment with Retrovir.

If you get any of these effects, and if they are severe, your physician may advise you to stop taking Retrovir.

As well as the effects listed below, other effects can develop during combination therapy for HIV.

→ It is important to read the information in "Other possible side effects of combination therapy for HIV".

Very common side effects

These may occur in **more than 1 in 10 people:**

- Headaches
- Nausea.

Common side effects

These may occur in **up to 1 in 10 people:**

- Vomiting
- Diarrhea
- Stomach pain
- Feeling dizzy
- Aching muscles
- Generally feeling unwell.

Common side effects that may show up in your blood tests are:

- A low red blood cell count (*anaemia*) or low white blood cell count (*neutropenia or leukopenia*)
- An increase in the level of liver enzymes
- An increased level in your blood of *bilirubin* (a substance produced in the liver) which may make your skin appear yellow.

Uncommon side effects

These may occur in **up to 1 in 100 people:**

- Skin rash (red, raised or itchy skin)
- Feeling breathless
- Fever
- General aches and pains
- Wind (flatulence)
- Weakness.

An uncommon side effect that may show up in your blood tests is:

- A decrease in the number of cells involved in blood clotting (*thrombocytopenia*), or in all kinds of blood cells (*pancytopenia*).

Rare side effects

These may occur in up **to 1 in 1,000 people:**

- Lactic acidosis (excess lactic acid in the blood; see below under "Other possible side effects of combination therapy for HIV")
- Liver disorders, such as jaundice, enlarged liver or fatty liver
- Inflammation of the pancreas
- Chest pain, disease of the heart muscle
- Fits (convulsions)
- Feeling depressed or anxious, not being able to sleep (insomnia), not being able to concentrate, feeling drowsy
- Indigestion, loss of appetite, taste disturbance
- Changes in the color of your nails, your skin, or the skin inside your mouth
- A flu-like feeling – chills, sweating and cough
- Tingly feelings in the skin (pins and needles)
- Passing urine more often
- Enlarged breasts in men.

A rare side effect that may show up in your blood tests is:

- A decrease in the number of a type of red blood cell (*pure red cell aplasia*).

Very rare side effects

A very rare side effects that may occur in **up to 1 in 10,000 people** and may show up in blood tests is:

- A failure of the bone marrow to produce new blood cells (*aplastic anaemia*).

Other possible side effects of combination therapy for HIV

Some other conditions may develop during HIV treatment.

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.

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, inform your physician immediately to receive the necessary treatment.

If you suffer any symptoms of infection while you are taking Retrovir:

→ **Tell your physician immediately.** Do not take other medicines for the infection without consulting with your physician.

Lactic acidosis is a rare but serious side effect

Some people taking Retrovir 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 (significantly overweight) people, primarily women.

Signs of lactic acidosis include:

- **Deep, rapid, difficult breathing**
- **Drowsiness**
- **Numbness** or **weakness** in the limbs
- **Loss of appetite, weight loss**
- **Nausea, vomiting**
- **Stomach pain.**

During treatment, the 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:

→ **Refer 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:

→ **Tell your physician.**

Other side effects may show up in tests

Combination therapy for HIV may also cause:

- **Increased levels of lactic acid** in the blood, which on rare occasions can lead to lactic acidosis.

This effect may show up in the blood tests you will have while you are taking Retrovir.

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

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking 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://sideeffects.health.gov.il/

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the physician.

Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

Store below 30°C. Protect from light. Keep the vial in the external carton.

6. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains –

Hydrochloric acid concentrated, sodium hydroxide, water for injection.

- What the medicine looks like and the contents of the package –

  Retrovir for Intravenous Infusion is a sterile, clear, nearly colourless, aqueous solution.

  The medicine comes in an amber glass 20 ml vial. Each carton contains 5 vials.
- License Holder: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.
- Manufacturer: Glaxo Operations UK Ltd., Barnard Castle, England.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 100-74-28753-00

Revised in October 2022 according to MOH guidelines.

The following information is intended for medical or healthcare professionals only:

RETROVIR IV for Infusion 10 mg/ml

SOLUTION FOR INFUSION

Zidovudine

DOSAGE AND ADMINISTRATION INFORMATION ONLY
Please refer to the Physician Leaflet for further information.

Pharmaceutical form
Solution for infusion.
Retrovir IV for Infusion is a clear, nearly colourless, sterile aqueous solution with a pH of approximately 5.5.

Posology and method of administration
The required dose of Retrovir IV for Infusion must be administered by slow intravenous infusion of the **diluted** product over a one-hour period.
Retrovir IV for Infusion must **NOT** be given intramuscularly.

***Dilution*:** Retrovir IV for Infusion **must** be diluted prior to administration (see Instructions for use and handling).

Dosage in adults
A dose for Retrovir IV for Infusion of 1 or 2 mg zidovudine/kg bodyweight every 4 hours provides similar exposure (AUC) to an oral dose of 1.5 or 3.0 mg zidovudine/kg every 4 hours (600 or 1,200 mg/day for a 70 kg patient).

The current recommended oral dose of Retrovir is 250 or 300 mg twice daily. This current dose is used as part of a multi-drug treatment regimen.

Patients should receive Retrovir IV for Infusion only until oral therapy can be administered.

Dosage in children
Limited data are available on the use of Retrovir IV for Infusion in children. A range of intravenous dosages between 80-160 mg/m^2 every 6 hours (320-640 mg/m^2/day) have been used. Exposure following the 120 mg/m^2 dose every 6 hours approximately corresponds to an oral dose of 180 mg/m^2 every 6 hours. An oral dose of Retrovir of 360 to 480 mg/m^2 per day approximately corresponds to an intravenous dose of 240-320 mg/m^2/day.

Dosage in the prevention of maternal-foetal transmission
Although the optimal dosage schedule has not been identified, the following dosage regimen has been shown to be effective. Pregnant women (over 14 weeks of gestation) should be given 500 mg/day orally (100 mg five times per day) until the beginning of labour. During labour and delivery, Retrovir should be administered intravenously at 2 mg/kg bodyweight given over one hour followed by a continuous intravenous infusion at 1 mg/kg/h until the umbilical cord is clamped.

The newborn infants should be given 2 mg/kg bodyweight orally every 6 hours starting within 12 hours after birth and continuing until 6 weeks old (e.g. a 3 kg neonate would require a 0.6 ml dose of oral solution every 6 hours). Infants unable to receive oral dosing should be given Retrovir intravenously at 1.5 mg/kg bodyweight infused over 30 minutes every 6 hours.

In case of planned caesarean, the infusion should be started 4 hours before the operation. In the event of false labour, the Retrovir infusion should be stopped and oral dosing restarted.

Dosage adjustments in patients with haematological adverse reactions
Substitution of zidovudine should be considered in patients whose haemoglobin level or neutrophil count fall to clinically significant levels. Other potential causes of anaemia or neutropenia should be excluded. Retrovir dose reduction or interruption should be considered in the absence of alternative treatments.

Dosage in the elderly
Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. However, since special care is advised in this age group due to age-associated changes such as the decrease in renal function and alterations in haematological parameters, appropriate monitoring of patients before and during use of Retrovir is advised.

Dosage in renal impairment
In patients with severe renal impairment, the recommended IV dosage is 1 mg/kg 3-4 times daily. This is equivalent to the current recommended oral daily dosage for this patient group of 300-400 mg allowing for oral bioavailability of 60-70%. Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. For patients with end-stage renal disease maintained on haemodialysis or peritoneal dialysis, the recommended dose is 100 mg every 6-8 hrs (300 mg-400 mg daily).

Dosage in hepatic impairment
Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage reductions may be necessary but, due to the large variability in zidovudine exposures in patients with moderate to severe liver disease, precise recommendations cannot be made. If monitoring of plasma zidovudine levels is not feasible, physicians will need to monitor for signs of intolerance, such as the development of haematological adverse reactions (anaemia, leucopenia, neutropenia) and reduce the dose and/or increase the interval between doses as appropriate.

Overdose
***Symptoms and signs*:**
No specific symptoms or signs have been identified following acute oral overdose with zidovudine, apart from those listed as undesirable effects.
Treatment: Patients should be observed closely for evidence of toxicity and given the necessary supportive therapy.

Haemodialysis and peritoneal dialysis appear to have a limited effect on elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

Shelf life and special precautions for storage
3 years when not stored above 30°C.

Instructions for use and handling
Dilution: Retrovir IV for Infusion must be diluted prior to administration. Since no antimicrobial preservative is included, dilution must be carried out under full aseptic conditions, preferably immediately prior to administration, and any unused portion of the vial should be discarded.

The required dose should be added to and mixed with Glucose Intravenous Infusion 5% w/v to give a final zidovudine concentration of either 2 mg/ml or 4 mg/ml. These dilutions are chemically and physically stable for up to 48 hours at both 5°C and 25°C.

Should any visible turbidity appear in the product either before or after dilution or during infusion, the preparation should be discarded.