Retrovir 10 mg / ml IV Concentrate for Solution for Infusion

zidovudine

Information for the patient

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Retrovir is and what it is used for

Retrovir is used to treat HIV (human immunodeficiency virus) infection.

The active ingredient in Retrovir is zidovudine. Retrovir is a type of medicine known as an anti-retroviral. It belongs to a group of 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 HIV in adults and children. To control your HIV infection, and to stop your illness getting worse, you must keep taking all your medicines.

If you're pregnant, your doctor may want you to take Retrovir, to help prevent you passing HIV on to your unborn baby. After the birth, your baby may be given Retrovir to help prevent it from getting infected with HIV.

HIV infection is spread by sexual contact with someone who's got the infection, or by transfer of infected blood (for example, by sharing injection needles).

2 What you need to know before you're given Retrovir

Don't take Retrovir:

- **if you're allergic** *(hypersensitive)* to zidovudine or any of the other ingredients of Retrovir (listed in Section 6)
- **if 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 with liver problems, including:

- some cases of *hyperbilirubinaemia* (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.

Take special care with Retrovir

Some people taking Retrovir or combination therapy for HIV are more at 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're seriously overweight** (especially if you're a woman)

➔ **Talk to your doctor if any of these applies to you**. You may need extra check-ups, including blood tests, while you're taking your medication. **See Section 4 for more information**.

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're taking Retrovir.

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

➔ **Talk to your doctor**.

Other medicines and Retrovir

Tell your doctor or pharmacist if you're taking any other medicines, or if you've taken any recently, including herbal medicines or other medicines you bought without a prescription.

Don't 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 can make it more likely that you'll 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 doctor** if you're taking any of these.

A medicine that interacts with Retrovir

- **phenytoin**, used for treating **epilepsy**.

➔ **Tell your doctor** if you're taking phenytoin. Your doctor may need to monitor you while you're taking Retrovir.

Pregnancy

If you are pregnant, if you become pregnant, or if you're planning to become pregnant:

➔ **Talk to your doctor** about the risks and benefits of taking Retrovir.

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

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

Breast-feeding is **not recommended** in women who are HIV-positive, because HIV infection can 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 breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible.**

Driving and using machines

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

➔ **Don't drive or operate machinery** unless you're feeling well.

You will need regular blood tests

For as long as you're taking Retrovir, your doctor will arrange regular blood tests to check for side effects. There's more information about these side effects in Section 4 of this leaflet.

Stay in regular contact with your doctor

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 your doctor**, and **don't stop taking Retrovir** without your doctor's advice.

Retrovir contains sodium

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

Retrovir IV vials contain latex

The rubber stopper of the IV vials contains latex.

➔ **Tell your doctor if you are allergic to latex.**

3 How Retrovir is given

Your doctor will give you this medicine by infusing it into a vein (a drip). It is diluted before use and is given slowly over a one-hour period. It 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.

How much Retrovir will you be given?

Adults and adolescents over 12 years old:

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

Children:

Your doctor will decide on the correct dose of Retrovir for your child, depending on the size of the child.

Pregnancy, childbirth and newborn babies:

You should not normally take Retrovir during the first 14 weeks of your 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 the labour and birth, your doctor 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 your doctor or pharmacist for advice**.

4 Possible 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 doctor 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 doctor should monitor for signs of lipoatrophy. Tell your doctor 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.

Like all medicines, this medicine can cause side effects, but not everyone gets them. Some side effects may show up in your blood tests, and may not appear until 4 to 6 weeks after you start taking Retrovir.

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

As well as the effects listed below, other conditions 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 affect **more than 1 in 10** people taking Retrovir:

- headaches
- feeling sick (nausea).

Common side effects

These may affect **up to 1 in 10** people taking Retrovir:

- being sick (vomiting)
- diarrhoea
- stomach pains
- 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 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 make your skin appear yellow.

Uncommon side effects

These may affect **up to 1 in 100** people taking Retrovir:

- skin rash (red, raised or itchy skin)
- feeling breathless
- fever (high temperature)
- general aches and pains
- wind (flatulence)
- weakness.

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

- 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 affect **up to 1 in 1000** people taking Retrovir:

- lactic acidosis (excess lactic acid in the blood; see the next section, '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 colour 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 effect that may affect **up to 1 in 10,000** people taking Retrovir, and may show up in blood tests is:

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

If you get any side effects

➔ **Talk to your doctor or pharmacist**. This includes any possible side effects not listed in this leaflet.

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 weak immune systems, 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, please inform your doctor immediately to seek necessary treatment.

If you get any symptoms of infection while you're taking Retrovir:

➔ **Tell your doctor immediately**. Don't take other medicines for the infection without your doctor's advice.

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 (very overweight) people, especially women.

Signs of lactic acidosis include:

- **deep, rapid, difficult breathing**
- **drowsiness**
- **numbness** or **weakness** in the limbs
- **loss of appetite, weight loss**
- **feeling sick** (nausea), **being sick** (vomiting)
- **stomach pain.**

During your treatment, your doctor will monitor you for signs of lactic acidosis. If you have any of the symptoms listed above, or any other symptoms that worry you:

➔ **See your doctor 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
- if they are also taking anti-inflammatory medicines called corticosteroids
- if they drink alcohol
- if their immune systems are very weak
- if 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 doctor**.

Other effects may show up in 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

This effect may show up in the blood tests you'll have while you're taking Retrovir.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Retrovir

Keep this medicine out of the sight and reach of children.

Keep the vials in the outer carton.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30 °C (86 °F).

6 Contents of the pack and other information

What Retrovir contains

The active substance is zidovudine. Each ml of concentrate for solution for infusion contains 10 mg of zidovudine.

The other ingredients are: water for injections, sodium hydroxide and/or hydrochloric acid.

What Retrovir looks like and contents of the pack

Retrovir 10 mg/ml IV Concentrate for Solution for Infusion is a clear, nearly colourless, sterile aqueous solution.

Retrovir 10 mg/ml IV Concentrate for Solution for Infusion is supplied in an amber glass 20 ml vial. Each carton contains 5 vials.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

ViiV Healthcare BV
Van Asch van Wijckstraat 55H
3811 LP Amersfoort
The Netherlands

Manufacturers

GlaxoSmithKline Manufacturing S.P.A.
Strada Provinciale Asolana No. 90
San Polo di Torrile 43056
Parma
Italy

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

Retrovir 10 mg / ml IV Concentrate for Solution for Infusion

zidovudine

DOSAGE AND ADMINISTRATION INFORMATION ONLY

Please refer to the Summary of Product Characteristics for further information

Pharmaceutical form

Concentrate for 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 1200 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 enhances 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.