PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

DOZRA 50 mg/5 ml ORAL SOLUTION, zidovudine 50 mg/5 ml.

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 further questions, please ask your doctor or your pharmacist.
- **DOZRA 50 mg/5 ml ORAL SOLUTION** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT DOZRA 50 mg/5 ml ORAL SOLUTION CONTAINS

The active substance is zidovudine. Each 5 ml contains Zidovudine 50 mg.

Contains sugar: 2160 mg sucrose per 5 ml.

The other ingredients are glycerin, strawberry cream flavour, purified water.

Preservative: Sodium benzoate 0,2 % *m/v.*

2. WHAT DOZRA ORAL SOLUTION IS USED FOR

DOZRA 50 mg/5 ml ORAL SOLUTION is indicated in combination with other antiretroviral agents for the treatment of Human Immunodeficiency Virus (HIV) infection in adults, children and mothers who are not breast-feeding.

3. BEFORE YOU TAKE DOZRA 50 mg/5 ml ORAL SOLUTION:

Do not take DOZRA 50 mg/5 ml ORAL SOLUTION:

- if you are hypersensitive (allergic) to zidovudine or any ingredients of **DOZRA 50 mg/5 ml ORAL SOLUTION**
- if you have abnormally low neutrophil cell counts (less than 0.75 x 10^9/litre).
- if you are taking stavudine and ribavirin.
- if you are **pregnant and or breastfeeding** your baby: Safety in pregnancy and lactation has not been established.

The long-term consequences of *in utero* and infant exposure to **DOZRA 50 mg/5 ml ORAL SOLUTION** are unknown.

Take special care with DOZRA 50 mg/5 ml ORAL SOLUTION:

- Pregnant women considering the use of **DOZRA 50 mg/5 ml ORAL SOLUTION** during pregnancy for prevention of HIV transmission to their infants should be advised that transmission might still occur despite therapy.
- To avoid the transmission of HIV to their infants, women infected with HIV should not breastfeed.
- If you became pregnant while taking **DOZRA 50 mg/5 ml ORAL SOLUTION** your baby may develop blood and nervous system disorders. Your doctor will monitor your baby's condition.
- **DOZRA 50 mg/5 ml ORAL SOLUTION** is not a cure for HIV infection and patients remain at risk of developing illnesses associated with immune suppression, including opportunistic infections and neoplasms.
- In patients with early HIV disease on long-term treatment the risk of lymphoma development is unknown as data on the development of neoplasms, including lymphomas are limited.
- Patients receiving combination therapy may also continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close observation by medical practitioners experienced in the treatment of patients with HIV-associated diseases.
- Blood parameters should be carefully monitored.
- You may develop a potentially fatal condition known as lactic acidosis while taking **DOZRA 50 mg/5 ml ORAL SOLUTION**. Inform your doctor or other healthcare professional immediately if you develop nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Your doctor will perform blood tests and treat you accordingly.
- Pancreatitis (inflammation of the pancreas) has been observed in some patients receiving **DOZRA 50 mg/5 ml ORAL SOLUTION**. Inform your doctor or other healthcare professional immediately if you develop abdominal pain, nausea or vomiting. Your doctor will discontinue treatment with **DOZRA 50 mg/5 ml ORAL SOLUTION** until the diagnosis of pancreatitis is excluded.
- You may develop liver problems when taking **DOZRA 50 mg/5 ml ORAL SOLUTION**. Inform your doctor or healthcare professional if you have any pre-existing liver disease including Hepatitis B or C.

  Do not stop taking **DOZRA 50 mg/5 ml ORAL SOLUTION** if you are co-infected with HIV and Hepatitis as this may cause the Hepatitis to worsen.

- You may develop a condition known as lipodystrophy while taking **DOZRA 50 mg/5 ml ORAL SOLUTION**. Inform your doctor or healthcare professional if you notice a change in the distribution of your body fat (e.g. accumulation of fat around the waist/stomach area, on the back of the neck and between the shoulders (buffalo hump), breast enlargement), wasting of the arms, legs and facial muscles, and increased blood glucose and lipid values.
- If you are taking **DOZRA 50 mg/5 ml ORAL SOLUTION** for the first time you may develop a condition known as Immune Reconstitution Inflammatory Syndrome (IRIS), within the first few months of treatment. This condition can cause opportunistic infections that are being treated to become worse or opportunistic diseases that were asymptomatic to be unmasked. Tell your doctor or healthcare professional if your general health worsens or if you think you may have an infection. You should not stop taking **DOZRA 50 mg/5 ml ORAL SOLUTION**. Your doctor will treat the infections appropriately.
- You may develop a condition known as osteonecrosis while taking **DOZRA 50 mg/5 ml ORAL SOLUTION**. Seek medical advice if you experience joint aches and pain, joint stiffness or difficulty in movement.
- You may continue to develop opportunistic infections and other complications of HIV infection while taking **DOZRA 50 mg/5 ml ORAL SOLUTION**. You should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.
- You are still at risk of transmitting HIV to others through sexual contact or blood contamination while taking current antiretroviral therapy including **DOZRA 50 mg/5 ml ORAL SOLUTION**. Appropriate precautions should continue to be employed.

Pregnancy and Breastfeeding:

Safety of **DOZRA 50 mg/5 ml ORAL SOLUTION** in pregnant and lactating women has not been established.

The long-term consequences of *in utero* and infant exposure to **DOZRA 50 mg/5 ml ORAL SOLUTION** are unknown.

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other health care professional for advice before taking **DOZRA 50 mg/5 ml ORAL SOLUTION**.

Taking other medicines with DOZRA 50 mg/5 ml ORAL SOLUTION:

Always tell your healthcare professional if you are taking any other medicine.

(This includes complementary or traditional medicines.)

- Caution must be exercised in the concomitant use of self-administered medicines. Consult your doctor/pharmacist.
- Phenytoin levels should be carefully monitored in patients by your doctor if you are receiving both medicines. There is a risk of either sub-therapeutic or toxic levels of phenytoin resulting from co-administration of these medicines.
- Aspirin, codeine, morphine, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone, and isoprinosine may alter the breakdown of zidovudine especially in chronic combination therapy.
- Concomitant therapy with potentially nephrotoxic, or myelosuppressive medicines, such as dapsone, systemic pentamidine, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine, and doxorubicin, may also increase the risk of toxicity with **DOZRA 50 mg/5 ml ORAL SOLUTION**.
- There is an *in vitro* antagonistic interaction between zidovudine and either ribavirin or stavudine. The concomitant use of either of these medicines with zidovudine should be avoided.
- Some patients receiving zidovudine may continue to experience opportunistic infections and concomitant use of prophylactic antimicrobial therapy may have to be considered. There is limited data that indicates no increased risk of toxicity with co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir.
- Renal excretion of the inactive glucuronide metabolite, and possibly zidovudine itself, is reduced in the presence of probenecid.
- Zidovudine has no effect on the pharmacokinetics of lamivudine.

[~~6.~~]4. HOW TO TAKE DOZRA 50 mg/5 ml ORAL SOLUTION:

Do not share medicines prescribed for you with any other person.

Always take DOZRA 50 mg/5 ml ORAL SOLUTION exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of DOZRA 50 mg/5 ml ORAL SOLUTION is too strong or too weak, talk to your doctor or pharmacist.

Recommended dosage in adults:

- *DOZRA 50 mg/5 ml ORAL SOLUTION in combination with other antiretroviral agents:*

  500 mg or 600 mg daily, orally in two or three divided doses.

  More than 1000 mg daily, orally in divided doses has been used. The effectiveness of dosages lower than 1000 mg daily in the treatment or prevention of HIV-associated neurological dysfunction is unknown.

- *For dosages of other antiretroviral agents used in combination therapy in advanced HIV infection:*

  Please consult the package inserts of the individual agents.

Recommended dosage in children 3 months to 12 years of age:

- *DOZRA 50 mg/5 ml ORAL SOLUTION in combination with other antiretroviral agents:*

  360 to 480 mg/m^2 daily, orally in three or four divided doses.

  For the treatment or prevention of HIV-associated neurological dysfunction, the effectiveness of dosages less than 720 mg/m^2 daily, i.e. 180 mg/m^2 every six hours is unknown.

  The maximum dosage should not exceed 200 mg every six hours.

Recommended dosage in the prevention of mother-to-foetus transmission:

- *Pregnant women over 14 weeks of gestation:*

  500 mg orally per day, i.e. 100 mg five times per day, until the beginning of labour. During labour and delivery zidovudine should be administered intravenously at 2 mg/kg body mass over 1 hour, followed by a continuous intravenous infusion at 1 mg/kg per hour until the umbilical cord is clamped.

- *The newborn infants: starting within 12 hours after birth until at 6 weeks of age:*

  2 mg/kg body mass orally every 6 hours. Infants unable to receive oral dosing should be given zidovudine intravenously at 1,5 mg/kg body mass, infused over 30 minutes every 6 hours.

Dosage adjustments in patients with haematological toxicity:

Dosage reduction or interruption of **DOZRA 50 mg/5 ml ORAL SOLUTION** therapy may be necessary in patients whose haemoglobin level falls to between 7,5 g/dℓ (4,65 mmol/ℓ) and 9 g/dℓ (5,59 mmol/ℓ) or whose neutrophil count falls to between 0,75 x 10^9/ℓ and 1,0 x 10^9/ℓ.

Dosage adjustments of DOZRA 50 mg/5 ml ORAL SOLUTION in combination with other antiretroviral medicines:

Dosage adjustments for each medicine should follow the dosing guidelines for the individual medicine.

For severe adverse events, where the causative agent is unclear, or those persisting after dose interruption or reduction of one medicine, the other medicine should also be interrupted or dose reduced.

The medical practitioner should refer to the package insert of the other antiretroviral medicines for a description of known adverse reactions.

Dosage in the elderly:

Zidovudine pharmacokinetics have not been studied in patients over 65 years of age and no specific data are available. Due to age-associated changes such as the decrease in renal function and alterations in haematological parameters in this age group, special care is advised with the use of **DOZRA 50 mg/5 ml ORAL SOLUTION**.

Appropriate monitoring of these patients before and during **DOZRA 50 mg/5 ml ORAL SOLUTION** therapy is advised.

Dosage in renal impairment:

Patients with advanced renal failure have a 50 % higher maximum plasma concentration of zidovudine compared to healthy individuals. Systemic exposure to zidovudine (measured as the area under the time-concentration curve) is increased 100 %; the half-life is not significantly altered. There is substantial accumulation of the major glucuronide metabolite in renal failure, but this does not appear to cause toxicity.

In patients with severe renal impairment on peritoneal or haemodialysis daily dosages of 300 mg to 400 mg in 3 to 4 divided dosages should be appropriate.

Haematological parameters and clinical response may influence the need for subsequent dosage adjustment. Haemodialysis and peritoneal dialysis have no significant effect on the elimination of zidovudine but enhance the elimination of the glucuronide metabolite.

Dosage in hepatic impairment:

There are only limited data available therefore precise dosage recommendations cannot be made, but dosage adjustments may be necessary. Data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Medical practitioners will need to monitor for signs of intolerance and adjust the dose and/or increase the interval between doses as appropriate.

If you take more DOZRA 50 mg/5 ml ORAL SOLUTION than you should:

Symptoms or signs such as fatigue, headache, vomiting, and reports of haematological disturbances, have been identified following acute over-dosage with zidovudine. Reported blood levels of zidovudine over 16 times the normal therapeutic level did not present with any short-term clinical, biochemical, or haematological sequelae in the patient.

Haemodialysis appears to have a limited effect on elimination of zidovudine but enhances the elimination of the inactive glucuronide metabolite.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take DOZRA 50 mg/5 ml ORAL SOLUTION:

Do not take a double dose to make up for forgotten individual doses.

5. POSSIBLE SIDE EFFECTS:

DOZRA 50 mg/5 ml ORAL SOLUTION can have side effects.

Blood and the lymphatic system disorders:

The most serious adverse reactions include anaemia, usually occurring after six weeks of therapy but occasionally earlier and often requiring transfusions; neutropenia, usually occurring at any time after 4 weeks of therapy but sometimes earlier; and leucopenia, which is usually secondary to neutropenia.

Thrombocytopenia, pancytopenia with marrow hypoplasia have also been reported.

Gastrointestinal disorders:

Nausea, vomiting, pigmentation of the oral mucosa, abdominal pain, dyspepsia, anorexia, diarrhoea, flatulence.

Hepato-billiary disorders:

Liver disorders such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin, pancreatitis.

Metabolism and nutritional disorders:

Lactic acidosis in the absence of hypoxia.

Musculoskeletal, connective tissue and bone disorders:

Myalgia, myopathy, asthenia.

Psychiatry disorders:

Anxiety, depression.

Skin and subcutaneous tissue disorders:

Nail and skin pigmentation, rash, urticaria, pruritis, sweating.

Respiratory, thoracic and mediastinal disorders:

Dyspnoea, cough, chest pain.

Nervous system disorders:

Headache, dizziness, insomnia, paraesthesia, somnolence, loss of mental acuity, convulsions.

Renal and urinary disorders:

Urinary frequency, gynaecomastia.

Reproductive system and breast disorders: Gynaecomastia.

General disorders and administrative site conditions:

Taste perversion, fever malaise, generalised pain, chills, influenza-like syndrome.

Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF DOZRA 50 mg/5 ml ORAL SOLUTION

Store at or below 30 °C. Keep the bottle tightly closed.

Store all medicines out of reach of children.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. PRESENTATION OF DOZRA 50 mg/5 ml ORAL SOLUTION

1. The solution is packed in a 300 ml round white opaque HDPE bottle closed with plastic screw cap containing expanded polyethylene wad and pilfer proof skirt.

Pack size: 240 ml of oral solution.

2. The solution is packed in a 250 ml round white opaque HDPE bottle closed with a polypropylene child resistant cap containing expanded polyethylene wad.

Pack size: 240 ml of oral solution.

3. The solution is packed in a 250 ml round white opaque HDPE bottle closed with a polypropylene child resistant closure with an induction sealing liner.

Pack size: 240 ml of oral solution.

A syringe is included in the pack.

8. IDENTIFICATION OF DOZRA 50 mg/5 ml ORAL SOLUTION

Colourless to pale yellow, strawberry flavoured liquid.

9. REGISTRATION NUMBER

A40/20.2.8/0562

10. NAME AND BUSINESS ADDRESS OF REGISTRATION HOLDER

Novagen Pharma

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene – Pretoria

(t) +27 12 345 3175

11. DATE OF PUBLICATION

Date of registration: 08 June 2007

Date of latest revision of the text as approved by Council: 08 June 2007

Date of notification with regard to amended Reg. 9 and 10: 02 February 2015