APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

BINDOLAM ORAL SOLUTION 10 mg/ml (Solution)

COMPOSITION:

Each ml contains:

Lamivudine 10 mg

Contains 200 mg sucrose.

Preservatives: Methylparaben 0.18 %

Propylparaben 0.02 %

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretroviral agents.

Symptoms may include generalised fatigue, nausea, vomiting, abdominal pain, and sudden unexplained weight loss, tachypnoea, dyspnoea, or motor weakness. Patients should be informed of the importance of early recognition of the symptoms of lactic acidosis. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.

Fatal and non-fatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, regardless of the degree of immunosuppression.

PHARMACOLOGICAL ACTION:

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication *in vitro,* including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to the active 5'-triphosphate which inhibits the RNA- and DNA-dependent activities of HIV reverse transcriptase by termination of the viral DNA chain. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content. *In vitro,* lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells. *In vitro,* lamivudine therefore has a high therapeutic index.

Reduced *in vitro* sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before.

Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture.

In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

Pharmacokinetics:

Pharmacokinetics in adults:

Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80 %. The mean time (T_{max}) to maximum serum concentration (C_{max}) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), C_{max} is in the order of 1-1.5 µg/ml.

The mean volume of distribution from intravenous studies has been reported as 1.3 l/kg and the mean terminal half-life of elimination as 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 l/kg/h, with predominantly renal clearance of more than 70 % via active tubular secretion, but little hepatic metabolism, at less than 10 %. The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes. A delay in T_{max} and reduction in C_{max} have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety.

Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.

Pharmacokinetics in children:

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability is reduced to approximately 65 %, in paediatric patients, with an increased clearance of 0.52 l/kg/hr.

There are limited pharmacokinetic data for patients < 3 months of age.

INDICATIONS:

BINDOLAM ORAL SOLUTION 10 mg/ml is indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children.

CONTRA-INDICATIONS:

Hypersensitivity to any of the ingredients.

WARNINGS AND SPECIAL PRECAUTIONS:

Patients receiving **BINDOLAM ORAL SOLUTION 10 mg/ml** and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.

Current antiretroviral therapy, including **BINDOLAM ORAL SOLUTION 10 mg/ml**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretroviral agents.

Symptoms may include generalised fatigue, nausea, vomiting, abdominal pain, and sudden unexplained weight loss, tachypnoea, dyspnoea, or motor weakness. Patients should be informed of the importance of early recognition of the symptoms of lactic acidosis. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with

other antiretroviral agents. The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk.

Fatal and non-fatal pancreatitis have occurred during therapy when stavudine was part of a combination regimen that included didanosine, with or without hydroxyurea, regardless of the degree of immunosuppression.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients.

Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS.

Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving [Proprietary Name] should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they 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.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including **BINDOLAM ORAL SOLUTION 10 mg/ml**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed**.**

Mitochondrial dysfunction

Nucleoside and nucleotide analogues have been demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or post-natally to nucleoside analogues. Apart from lactic acidosis/hyperlactataemia (see above) other manifestations of mitochondrial dysfunction include haematological disorders (anaemia, neutropenia), and peripheral neuropathy. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behaviour). It is not known whether the neurological disorders are transient or permanent. Any foetus exposed in utero to nucleoside and nucleotide analogues, even HIV negative infants/children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant sign and symptoms.

Pancreatitis:

Pancreatitis has been observed in some patients receiving **BINDOLAM ORAL SOLUTION 10 mg/ml**. However it is unclear whether this is due to **BINDOLAM ORAL SOLUTION 10 mg/ml** or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **BINDOLAM ORAL SOLUTION 10 mg/ml** until diagnosis of pancreatitis is excluded.

Lactic acidosis / hyperlactataemia

Use of **BINDOLAM ORAL SOLUTION 10 mg/ml** can result in potentially fatal lactic acidosis as a consequence of mitochondrial dysfunction. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and the serum bicarbonate and respond as follows:

- Lactate 2-5 mmol/ℓ with minimum symptoms: switch to agents that are less likely to cause lactic acidosis.
- Lactate 5-10 mmol/ℓ with symptoms and/or with reduced standard bicarbonate: Stop NRTIs and change treatment option. Once lactate has settled, use medicines that are less likely to cause lactic acidosis. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis and hyperthyroidism.
- Lactate> 10 mmol/ℓ: STOP all therapy (80 % mortality). The above lactate values may not be applicable to paediatric patients. Caution should be exercised when administering **BINDOLAM ORAL SOLUTION 10 mg/ml** to patients with known risk factors for liver disease. Treatment with **BINDOLAM ORAL SOLUTION 10 mg/ml** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance. The dose should therefore be adjusted (see **Dosage and Directions for Treatment**).

Liver disease

Use of **BINDOLAM ORAL SOLUTION 10 mg/ml** can result in hepatomegaly due to non-alcoholic fatty liver disease (hepatic steatosis). The safety and efficacy of **BINDOLAM ORAL SOLUTION 10 mg/ml** has not been established in patients with significant underlying liver disorders/diseases. In case of concomitant antiviral therapy for hepatitis B or C, please also consult the relevant package inserts for these medicines. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored. If there is evidence of worsening liver disease in such patients, temporary or permanent discontinuation of treatment must be considered. Patients with HIV and hepatitis B or C virus co-infection Patients with chronic hepatitis B or C and treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Medical practitioners should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co-infected with hepatitis B virus (HBV). In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant package inserts for these medicines. Patients co-infected with HIV and HBV who discontinue **BINDOLAM ORAL SOLUTION 10 mg/ml** should be closely monitored with both clinical and laboratory follow-up after stopping treatment. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Discontinuation of **BINDOLAM ORAL SOLUTION 10 mg/ml** therapy in patients co-infected with HIV and HBV may be associated with severe, acute exacerbations of hepatitis.

Ability to Drive and Use Machines

There is no data to suggest that the ability to drive and operate heavy machinery may be impaired.

INTERACTIONS:

Zidovudine plasma levels are not significantly altered when co-administered with **BINDOLAM ORAL SOLUTION 10 mg/ml**. (See **Pharmacokinetics**).

An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment.

Administration of co-trimoxazole with the **BINDOLAM ORAL SOLUTION 10 mg per ml**/zidovudine combination in patients with renal impairment should be carefully assessed. **BINDOLAM ORAL**

SOLUTION 10 mg/ml may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. **BINDOLAM ORAL SOLUTION 10 mg/ml** is therefore, not recommended to be used in combination with zalcitabine.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults and adolescents more than 12 years of age:

The recommended dose of **BINDOLAM ORAL SOLUTION 10 mg/ml** is 300 mg daily. This may be administered as either 300 mg once daily or 150 mg twice daily.

The package insert for zidovudine must be consulted for information on its dosage and administration.

For patients with low body weights (less than 50 kg), the recommended oral dose of **BINDOLAM ORAL SOLUTION 10 mg/ml** is 2 mg/kg twice daily.

Children ≥ 3 months to 12 years of age:

The recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.

Children < 3 months of age:

There is a limited data to propose specific dosage recommendations (see **Pharmacokinetics**).

BINDOLAM ORAL SOLUTION 10 mg/ml can be taken with or without food.

Renal and Hepatic Impairment:

Renal impairment, whether disease- or age-related, affects lamivudine elimination. For recommended dosage regimens in patients with a creatinine clearance below 50 ml/min see table below:

Adults and adolescents > 12 years of age:

Creatinine Clearance (ml/min)	Recommended dose of BINDOLAM ORAL SOLUTION 10 mg/ml
≥ 50	150 mg twice daily
30 - 49	150 mg once daily
15 - 29	150 mg first dose, then 100 mg once daily
5 - 14	150 mg first dose, then 50 mg once daily
< 5	50 mg first dose, then 25 mg once daily

Children > 3 months to 12 years:

Creatinine Clearance (ml/min)	Recommended dose of BINDOLAM ORAL SOLUTION 10 mg/ml
≥ 50	4 mg/kg first dose, then 4 mg/kg twice daily
30 - 49	4 mg/kg first dose, then 4 mg/kg twice daily
15 - 29	4 mg/kg first dose, then 2.6 mg/kg twice daily
5 - 14	4 mg/kg first dose, then 1.3 mg/kg once daily
< 5	1.3 mg/kg first dose, then 0.7 mg/kg once daily

SIDE-EFFECTS:

The following side-effects have been reported during therapy of HIV disease with **BINDOLAM ORAL SOLUTION 10 mg/ml** alone, and in combination with other anti-retrovirals.

Gastro-intestinal disorders:

Frequent:

Upper abdominal pain, diarrhoea, nausea, vomiting, pancreatitis

Blood and the lymphatic system disorders:

Less frequent:

Neutropenia, anaemia

Frequency not known:

Thrombocytopenia

Skin and subcutaneous tissue disorders:

Frequency not known:

Alopecia

Nervous system disorders:

Frequent:

Headache, peripheral neuropathy, paraesthesia

Musculoskeletal, connective tissue and bone disorders:

Frequent:

Arthralgia

Frequency not known:

Muscle disorders, including rhabdomyolysis

General disorders and administrative site conditions:

Frequent:

Malaise, fatigue

Frequency not known:

Fever

Immune system disorders:

Frequent:

Skin rash

Investigations:

Frequency not known:

Transient rises in serum liver enzymes (AST, ALT) and rises in serum amylase have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment is symptomatic and supportive.

IDENTIFICATION:

A clear, colourless to pale yellow, strawberry-banana flavoured liquid in 250 ml round white opaque HDPE bottle.

PRESENTATION:

1. The solution is packed in a 300 ml round white opaque HDPE bottle closed with a plastic screw cap containing an expanded polyethylene wad and a 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 an 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 having induction sealing liner.

Pack size: 240 ml of oral solution

A measuring Syringe is incorporated along with the bottle.

STORAGE INSTRUCTIONS:

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

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:

BINDOLAM ORAL SOLUTION 10 mg/ml: 42/20.2.8/1093

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Aurobindo Pharma (Pty) Ltd.

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