

#### PRESENTATION:

Tivizid® Tablet: Each film-coated tablet contains the active ingredients 300 mg of Abacavir (as Abacavir Sulfate INN), 150 mg of Lamivudine USP, and 300 mg of Zidovudine BP.

#### PHARMACOLOGY:

**Abacavir:** Abacavir is a carbocyclic synthetic nucleoside analogue. Intracellularly, Abacavir is converted by cellular enzymes to the active metabolite, carbovir triphosphate. Carbovir triphosphate inhibits the activity of HIV reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. Following oral administration, abacavir is rapidly absorbed and extensively distributed. Binding of abacavir to human plasma proteins is approximately 50%. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase to form the 5'-carboxylic acid and glucuronyl transferase to form the 5'-glucuronide.

**Lamivudine:** Intracellularly, Lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of RT via DNA chain termination after incorporation of the nucleoside analogue. Following oral administration, Lamivudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low.

**Zidovudine:** Intracellularly, Zidovudine is phosphorylated to its active 5'-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of RT via DNA chain termination after incorporation of the nucleoside analogue. Following oral administration, Zidovudine is rapidly absorbed and extensively distributed. Binding to plasma protein is low. Zidovudine is eliminated primarily by hepatic metabolism.

#### INDICATION AND USES:

Tivizid® is indicated alone or in combination with other antiretroviral agents for the treatment of HIV infection.

#### DOSAGE AND ADMINISTRATION:

The recommended oral dose of Tivizid® for adults and adolescents is 1 tablet twice daily. Tivizid® is not recommended in adults or adolescents who weigh less than 40 kg because it is a fixed-dose tablet.

#### CONTRAINDICATION:

Tivizid® tablets are contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product

#### WARNING:

**Hypersensitivity Reaction:** This combination contains abacavir sulfate, which has been associated with fatal hypersensitivity reactions. Patients developing signs or symptoms of hypersensitivity should discontinue this combination as soon as a hypersensitivity reaction is first suspected, and should seek medical evaluation immediately.

**Bone Marrow Suppression:** Since this combination contains Zidovudine, it should be used with caution in patients who have bone marrow compromise evidenced by

granulocyte count  $<1,000$  cells/mm<sup>3</sup> or hemoglobin  $<9.5$  g/dL. Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with this combination. For HIV-infected individuals and patients with asymptomatic or early HIV disease, periodic blood counts are recommended.

**Myopathy:** Myopathy and myositis, with pathological changes similar to that produced by HIV disease, have been associated with prolonged use of Zidovudine, and therefore may occur with therapy with this combination.

**Post-treatment Exacerbations of Hepatitis:** In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B (HBV), clinical and laboratory evidence of exacerbations of hepatitis after discontinuation of Lamivudine. Patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

#### **ADVERSE ACTION AND PRECAUTION:**

The potential for cross-resistance between abacavir and other NRTIs should be considered when choosing new therapeutic regimens in therapy-experienced patients.

**Patients with HIV and Hepatitis B Virus Coinfection:**

**Lamivudine:** Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV.

**Patients with Impaired Renal Function:**

**Abacavir, Lamivudine and Zidovudine:** Since this combination is a fixed-dose tablet and the dosage of the individual components cannot be altered, patients with creatinine clearance  $<50$  mL/min should not receive this tablet.

**Fat Redistribution:**

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy.

#### **DRUG INTERACTION:**

No clinically significant changes to pharmacokinetic parameters were observed for Abacavir, Lamivudine, or Zidovudine when administered together.

**Abacavir:** Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure.

**Lamivudine:** Trimethoprim (TMP) 160 mg/sulfamethoxazole (SMX) 800 mg once daily has been shown to increase Lamivudine exposure (AUC). The effect of higher doses of TMP/SMX on Lamivudine pharmacokinetics has not been investigated.

Lamivudine and Zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of this combination in combination with zalcitabine is not recommended.

**Zidovudine:** Coadministration of ganciclovir, interferon-alpha, and other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of zidovudine.

Concomitant use of zidovudine with stavudine should be avoided since an antagonistic relationship has been demonstrated in vitro. In addition, concomitant use of zidovudine with doxorubicin or ribavirin should be avoided because an antagonistic relationship has also been demonstrated in vitro.

#### **USE IN PREGNANCY AND LACTATION:**

**Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies of abacavir / Lamivudine / Zidovudine in pregnant women. This drug should be used during pregnancy only if the potential benefits outweigh the risks.

**Nursing Mothers:** The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV infection.

**Abacavir, Lamivudine, and Zidovudine:** Zidovudine is excreted in breast milk; abacavir and lamivudine are secreted into the milk of lactating rats.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving this combination.

**PAEDIATRIC USE:**

This combination is not intended for use in pediatric patients. This combination tablet should not be administered to adolescents who weigh less than 40 kg because it is a fixed-dose tablet that cannot be adjusted for this patient population.

**STORAGE CONDITION:**

Store at a dry and cool place. Protect from light and moisture.  
Keep the medicine out of the reach of children.

**HOW SUPPLIED:**

Tivizid ® Tablet: Each box contains 1x10 tablets in blister pack.