

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**21-205/S-003, S-004**

**ADMINISTRATIVE AND CORRESPONDENCE**  
**DOCUMENTS**



## Memorandum of Project Manager's Review: Final Printed Labeling

**NDA:** 21-205/S-003 and S-004

**Drug:** Trizivir® (abacavir sulfate, lamivudine, and zidovudine) tablets

**Sponsor:** GlaxoSmithKline  
5 Moore Drive  
Research Triangle Park, NC 27709

**Date Completed** May 24, 2002

**Submission Date** October 17, 2001/S-003  
February 7, 2002/S-004

### Materials Reviewed

1. Final printed labeling (FPL) dated February 7, 2002: S-004
2. FPL dated October 17, 2001: S-003
3. FPL approved on February 5, 2002: S-002

### Background

The purpose of these "Special Supplements - Changes Being Effected" is to update the Trizivir tablets label to reflect recently approved changes made to the Ziagen (abacavir sulfate), Epivir (lamivudine), and Retrovir (zidovudine) labeling.

The final printed labeling (FPL) dated February 7, 2002 was electronically compared to the FPL (S-002) dated May 3, 2001, which was approved on February 5, 2002.

### NDA 21-205/S-003

The Special Supplement – "Changes Being Effected" dated October 17, 2001 (S-003) updates the **CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections of the Trizivir tablets label. Specifically, these revisions include changes recently approved for supplemental New Drug Applications for Epivir (lamivudine) products. These included the following supplements:

#### **Epivir Tablets and Epivir Oral Solution**

NDA 20-564/S-011 and NDA 20-596/S-012, approved January 5, 2001;  
NDA 20-564/S-012 and NDA 20-596/S-013, approved March 6, 2001; and  
NDA 20-564/S-013 and NDA 20-596/S-014, approved June 19, 2001.

In addition, S-003 includes revisions for the following supplemental New Drug Applications for Retrovir (zidovudine) products:

**Retrovir Capsules, Tablets, and Syrup**

NDA 19-655/S-037, NDA 20-518/S-009 and NDA 19-910/S-025 FPL dated August 7, 2001.

The ADVERSE REACTIONS: *Observed During Clinical Practice* section has been updated to include events recently added to the labeling for Retrovir (cardiomyopathy, gynecomastia, oral mucosa pigmentation, Epivir (stomatitis, weakness, anemia, lymphadenopathy, splenomegaly, post-treatment exacerbation of hepatitis B, paresthesia, peripheral neuropathy, abnormal breath sounds/wheezing), and Epivir-HBV (pure red cell aplasia).

**The following language was added in S-003:**

1. **CLINICAL PHARMACOLOGY: SPECIAL POPULATIONS: "Impaired Hepatic Function: TRIZIVIR:** A reduction in the daily dose of zidovudine may be necessary in patients with mild to moderate impaired hepatic function or liver cirrhosis. Because TRIZIVIR is a fixed-dose combination that cannot be adjusted for this patient population, TRIZIVIR is not recommended for patients with impaired hepatic function."
2. **WARNINGS: "Posttreatment 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 have occurred after discontinuation of lamivudine. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events appear to have been self-limited, fatalities have been reported in some cases. Similar events have been reported from post-marketing experience after changes from lamivudine-containing HIV treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory followup for at least several months after stopping treatment. There is insufficient evidence to determine whether re-initiation of lamivudine alters the course of posttreatment exacerbations of hepatitis."
3. **PRECAUTIONS: Patients with HIV and Hepatitis B Virus Coinfection:** was revised to read:  
"Lamivudine: Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. In non-HIV-infected patients treated with lamivudine for chronic hepatitis B, emergence of lamivudine-resistant HBV has been detected and has been associated with diminished treatment response (see EPIVIR-HBV package insert for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been reported in HIV-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus."
4. **PRECAUTIONS: Drug Interactions: Lamivudine:** was revised to read:  
"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 (see

CLINICAL PHARMACOLOGY). Lamivudine and zalcitabine may inhibit the intracellular phosphorylation of one another. Therefore, use of TRIZIVIR in combination with zalcitabine is not recommended.”

5. **PRECAUTIONS: Pregnancy:** was revised to read:

**Pregnancy:**

Pregnancy Category C. There are no adequate and well-controlled studies of TRIZIVIR in pregnant women. Reproduction studies with abacavir, lamivudine, and zidovudine have been performed in animals (see Abacavir, Lamivudine, and Zidovudine sections below). TRIZIVIR should be used during pregnancy only if the potential benefits outweigh the risks.

**Abacavir:** Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta. Developmental toxicity (depressed fetal body weight and reduced crown-rump length) and increased incidences of fetal anasarca and skeletal malformations were observed when rats were treated with abacavir at a dose 35 times higher than the human exposure, based on AUC (1000 mg/kg per day). In a fertility study, evidence of toxicity to the developing embryo and fetuses (increased resorptions, decreased fetal body weights) occurred only at 500 mg/kg per day. The offspring of female rats treated with abacavir at 500 mg/kg per day (beginning at embryo implantation and ending at weaning) showed increased incidence of stillbirth and lower body weights throughout life. In the rabbit, there was no evidence of drug-related developmental toxicity and no increases in fetal malformations at doses up to 8.5 times the human exposure, based on AUC.

**Lamivudine:** Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta. Reproduction studies with orally administered lamivudine have been performed in rats and rabbits at doses up to 4000 mg/kg per day and 1000 mg/kg per day, respectively, producing plasma levels up to approximately 35 times that for the adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of early embryolethality was seen in the rabbit at exposure levels similar to those observed in humans, but there was no indication of this effect in the rat at exposure levels up to 35 times that in humans.

**Zidovudine:** Reproduction studies with orally administered zidovudine in the rat and in the rabbit at doses up to 500 mg/kg per day revealed no evidence of teratogenicity with zidovudine. Zidovudine treatment resulted in embryo/fetal toxicity as evidenced by an increase in the incidence of fetal resorptions in rats given 150 or 450 mg/kg per day and rabbits given 500 mg/kg per day. The doses used in the teratology studies resulted in peak zidovudine plasma concentrations (after one half of the daily dose) in rats 66 to 226 times, and in rabbits 12 to 87 times, mean steady-state peak human plasma concentrations (after one sixth of the daily dose) achieved with the recommended daily dose (100 mg every 4 hours). In an additional teratology study in rats, a dose of 3000 mg/kg per day (very near the oral median lethal dose in rats of approximately 3700 mg/kg) caused marked maternal toxicity and an increase in the incidence of fetal malformations. This dose resulted in peak zidovudine plasma concentrations 350 times peak human plasma concentrations. No evidence of teratogenicity was seen in this experiment at doses of 600 mg/kg per day or less. Two rodent carcinogenicity studies were conducted (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

**Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant women exposed to TRIZIVIR or other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

**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 TRIZIVIR.

**NDA 21-205/S-004**

The Special Supplement – Changes Being Effected” dated February 7, 2002 (S-004) updates the labeling for Trizivir tablets to add Stevens-Johnson syndrome language under the **ADVERSE REACTIONS: Observed During Clinical Practice** subsection, as requested by the Division. This supplement also adds language in the Carcinogenesis and Animal Toxicity sections, as approved for the Ziagen label (NDA 20-977/S-005 and NDA 20-978/S-006). Aplastic anemia was added to the Hemtic and Lymphatic

subsection to concur with the Retrovir label (NDA 19-655/S-032, NDA 19-910/S-021, and NDA 20-518/S-004).

**The following language was added in S-004:**

1. **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility:** was revised to read:

*“Carcinogenicity:*

*Abacavir:* Abacavir was administered orally at 3 dosage levels to separate groups of mice (60 females and 60 males per group) and rats (56 females and 56 males in each group) in carcinogenicity studies. Single doses were 55, 110, and 330 mg/kg per day in mice and 30, 120, and 600 mg/kg per day in rats. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats.

*Lamivudine:* Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.”

2. **ADVERSE REACTIONS: Observed During Clinical Practice:** now reads:

“The following events have been identified during post-approval use of abacavir, lamivudine, and/or zidovudine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to lamivudine and/or zidovudine.

*Abacavir:* Suspected Stevens-Johnson syndrome (SJS) has been reported in patients receiving abacavir in combination with medications known to be associated with SJS. Because of the overlap of clinical signs and symptoms between hypersensitivity to abacavir and SJS, and the possibility of multiple drug sensitivities in some patients, abacavir should be discontinued and not restarted in such cases.

*Lamivudine and Zidovudine:*

*Cardiovascular:* Cardiomyopathy.

*Digestive:* Stomatitis.

*Endocrine and Metabolic:* Gynecomastia, hyperglycemia.

*Gastrointestinal:* Oral mucosal pigmentation.

*General:* Vasculitis, weakness.

*Hemic and Lymphatic:* Aplastic anemia, anemia, lymphadenopathy, pure red cell aplasia, splenomegaly.

*Hepatic and Pancreatic:* Lactic acidosis and hepatic steatosis, pancreatitis, posttreatment exacerbation of hepatitis B (see WARNINGS).

*Hypersensitivity:* Sensitization reactions (including anaphylaxis), urticaria.

*Musculoskeletal:* Muscle weakness, CPK elevation, rhabdomyolysis.

*Nervous:* Paresthesia, peripheral neuropathy, seizures.

*Respiratory:* Abnormal breath sounds/wheezing.

*Skin:* Alopecia, erythema multiforme, Stevens-Johnson syndrome.”

**\*Please note that separate revisions to the ADVERSE REACTIONS: Observed During Clinical Practice section were made in both S-003 and S-004, and all changes are reflected above.**

3. **"ANIMAL TOXICOLOGY:** Myocardial degeneration was found in mice and rats following administration of abacavir for 2 years. The systemic exposures were equivalent to 7 to 24 times the expected systemic exposure in humans. The clinical relevance of this finding has not been determined."

#### **Additional Revisions**

1. In the **DESCRIPTION** section, under **Abacavir Sulfate**, the third paragraph is now indented three spaces.
2. In the **CLINICAL PHARMACOLOGY**, under **Effect of Food on Absorption of TRIZIVIR**, a comma was added after "lamivudine" in the third sentence.

#### **Summary**

The revisions to the Trizivir tablets labeling are acceptable. Please refer to the medical officer's signature for concurrence. An approval letter will be issued to the applicant.

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Virginia L. Yoerg  
Regulatory Health Project Manager  
Division of Antiviral Drug Products

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Virginia Yoerg  
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CSO

Harc copy already signed off. CSO review for Trizivir CBES.

Tony DeCicco  
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