

**Table 3. Outcomes of Randomized Treatment Through 48 Weeks  
(Intent-to-Treat)**

Outcome	EPIVIR 300 mg Once Daily plus RETROVIR plus Efavirenz (n = 278)	EPIVIR 150 mg Twice Daily plus RETROVIR plus Efavirenz (n = 276)
Responder*	67%	65%
Virologic failure <sup>†</sup>	8%	8%
Discontinued due to clinical progression	<1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons <sup>‡</sup>	18%	14%

\* Achieved confirmed plasma HIV-1 RNA <400 copies/mL and maintained through 48 weeks.

<sup>†</sup> Achieved suppression but rebounded by Week 48, discontinued due to virologic failure, insufficient viral response according to the investigator, or never suppressed through Week 48.

<sup>‡</sup> Includes consent withdrawn, lost to followup, protocol violation, data outside the study-defined schedule, and randomized but never initiated treatment.

The proportions of patients with HIV-1 RNA <50 copies/mL (via Roche Ultrasensitive assay) through Week 48 were 61% for patients receiving EPIVIR 300 mg once daily and 63% for patients receiving EPIVIR 150 mg twice daily. Median increases in CD4+ cell counts were 144 cells/mm<sup>3</sup> at Week 48 in patients receiving EPIVIR 300 mg once daily and 146 cells/mm<sup>3</sup> for patients receiving EPIVIR 150 mg twice daily.

A small, randomized, open-label pilot study, EPV40001, was conducted in Thailand. A total of 159 treatment-naive adult patients (male 32%, Asian 100%, median age 30 years, baseline median CD4 cell count 380 cells/mm<sup>3</sup>, median plasma HIV-1 RNA 4.8 log<sub>10</sub> copies/mL) were enrolled. Two of the treatment arms in this study provided a comparison between lamivudine 300 mg once daily (n = 54) and lamivudine 150 mg twice daily (n = 52), each in combination with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses of 48-week data, the proportions of patients with HIV-1 RNA below 400 copies/mL were 61% (33/54) in the group randomized to once-daily lamivudine and 75% (39/52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies/mL were 54% (29/54) in the once-daily lamivudine group and 67%

(35/52) in the all twice-daily group; and the median increases in CD4 cell counts were 166 cells/mm<sup>3</sup> in the once-daily lamivudine group and 216 cells/mm<sup>3</sup> in the all twice-daily group.

**Clinical Endpoint Study in Pediatric Patients:** ACTG300 was a multicenter, randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR<sup>®</sup> (zidovudine) to didanosine monotherapy. A total of 471 symptomatic, HIV-infected therapy-naïve (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4 cell count was 868 cells/mm<sup>3</sup> (mean: 1,060 cells/mm<sup>3</sup> and range: 0 to 4,650 cells/mm<sup>3</sup> for patients ≤5 years of age; mean 419 cells/mm<sup>3</sup> and range: 0 to 1,555 cells/mm<sup>3</sup> for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 log<sub>10</sub> copies/mL. The median duration on study was 10.1 months for the patients receiving EPIVIR plus RETROVIR and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 4.

**Table 4. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)**

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV disease progression or death (total)	15 (6.4%)	37 (15.7%)
Physical growth failure	7 (3.0%)	6 (2.6%)
Central nervous system deterioration	4 (1.7%)	12 (5.1%)
CDC Clinical Category C	2 (0.8%)	8 (3.4%)
Death	2 (0.8%)	11 (4.7%)

## CONTRAINDICATIONS

EPIVIR Tablets and Oral Solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the products.

## WARNINGS

**In pediatric patients with a history of prior antiretroviral nucleoside exposure, a history of pancreatitis, or other significant risk factors for the development of pancreatitis, EPIVIR should be used with caution. Treatment with EPIVIR should be stopped immediately if clinical signs, symptoms, or laboratory abnormalities suggestive of pancreatitis occur (see ADVERSE**

**REACTIONS).**

**Lactic Acidosis/Severe Hepatomegaly with Steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine and other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering EPIVIR to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with EPIVIR should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

**Important Differences Among Lamivudine-Containing Products:** EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) than in EPIVIR-HBV Tablets and Oral Solution. EPIVIR-HBV was developed for patients with chronic hepatitis B. The formulation and dosage of lamivudine in EPIVIR-HBV are not appropriate for patients dually infected with HIV and HBV. Lamivudine has not been adequately studied for treatment of chronic hepatitis B in patients dually infected with HIV and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV infection, rapid emergence of HIV resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV treatment. If a decision is made to administer lamivudine to patients dually infected with HIV and HBV, EPIVIR Tablets, EPIVIR Oral Solution, or COMBIVIR<sup>®</sup> (lamivudine/zidovudine) Tablets should be used as part of an appropriate combination regimen. COMBIVIR (a fixed-dose combination tablet of lamivudine and zidovudine) should not be administered concomitantly with EPIVIR, EPIVIR-HBV, RETROVIR, or TRIZIVIR<sup>®</sup>.

**Posttreatment Exacerbations of Hepatitis:** In clinical trials in non-HIV-infected patients treated with lamivudine for chronic hepatitis B, 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.

## PRECAUTIONS

**Patients with Impaired Renal Function:** Reduction of the dosage of EPIVIR is recommended for patients with impaired renal function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**Patients with HIV and Hepatitis B Virus Coinfection:** 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. Posttreatment exacerbations of hepatitis have also been reported (see WARNINGS).

**Differences Between Dosing Regimens:** Trough levels of lamivudine in plasma and of intracellular lamivudine triphosphate were lower with once-daily dosing than with twice-daily dosing (see CLINICAL PHARMACOLOGY). The clinical significance of this observation is not known.

**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. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

**Information for Patients:** EPIVIR is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using EPIVIR. Patients should be advised that the use of EPIVIR has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised that EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV Tablets and Oral Solution. If a decision is made to include lamivudine in the HIV treatment regimen of a patient dually infected with HIV and HBV, the

formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used.

Patients should be advised that the long-term effects of EPIVIR are unknown at this time.

EPIVIR Tablets and Oral Solution are for oral ingestion only.

Patients should be advised of the importance of taking EPIVIR with combination therapy on a regular dosing schedule and to avoid missing doses.

Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time.

**Drug Interactions:** TMP 160 mg/SMX 800 mg once daily has been shown to increase lamivudine exposure (AUC) by 44% (see CLINICAL PHARMACOLOGY). No change in dose of either drug is recommended. There is no information regarding the effect on lamivudine pharmacokinetics of higher doses of TMP/SMX such as those used to treat *Pneumocystis carinii* pneumonia. No data are available regarding the potential for interaction with other drugs that have renal clearance mechanisms similar to that of lamivudine.

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

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** 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. Lamivudine was not active in a microbial mutagenicity screen or an in vitro cell transformation assay, but showed weak in vitro mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of in vivo genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg per day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

**Pregnancy:** Pregnancy Category C. Reproduction studies have been performed in rats and rabbits at orally administered doses up to 4,000 mg/kg/day and 1,000 mg/kg/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 embryoletality 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. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

In 2 clinical studies conducted in South Africa, pharmacokinetic measurements were performed on samples from pregnant women who received lamivudine beginning at week 38 of gestation (10 women who received 150 mg twice daily in combination with zidovudine and 10 who received lamivudine 300 mg twice daily without other antiretrovirals) or beginning at week 36 of gestation (16 women who received lamivudine 150 mg twice daily in combination with zidovudine). These studies were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in the pregnant women were similar to those obtained following birth and in non-pregnant adults. Lamivudine concentrations were generally similar in maternal, neonatal, and cord serum samples. In a subset of subjects from whom amniotic fluid specimens were obtained following natural rupture of membranes, amniotic fluid concentrations of lamivudine ranged from 1.2 to 2.5 mcg/mL (150 mg twice daily) and 2.1 to 5.2 mcg/mL (300 mg twice daily) and were typically greater than 2 times the maternal serum levels. See the ADVERSE REACTIONS section for the limited late-pregnancy safety information available from these studies. Lamivudine should be used during pregnancy only if the potential benefits outweigh the risks.

**Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant women exposed to lamivudine, a 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.**

A study in lactating rats administered 45 mg/kg of lamivudine showed that lamivudine concentrations in milk were slightly greater than those in plasma. Lamivudine is also excreted in human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

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 lamivudine.**

**Pediatric Use: HIV:** Limited, uncontrolled pharmacokinetic and safety data are available from

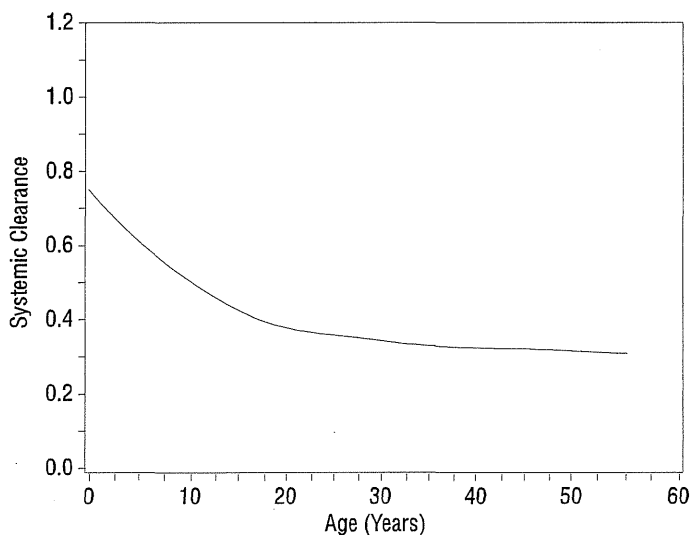
administration of lamivudine (and zidovudine) to 36 infants up to 1 week of age in 2 studies in South Africa. In these studies, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric patients (>3 months of age) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age ranges >3 months old. See the ADVERSE REACTIONS section for the limited safety information available from these studies.

The safety and effectiveness of twice-daily EPIVIR in combination with other antiretroviral agents have been established in pediatric patients 3 months of age and older.

In Study A2002, pharmacokinetic properties of lamivudine were assessed in a subset of 57 HIV-infected pediatric patients (age range: 4.8 months to 16 years, weight range: 5 to 66 kg) after oral and IV administration of 1, 2, 4, 8, 12, and 20 mg/kg/day. In the 9 infants and children (range: 5 months to 12 years of age) receiving oral solution 4 mg/kg twice daily (the usual recommended pediatric dose), absolute bioavailability was  $66\% \pm 26\%$  (mean  $\pm$  SD), which was less than the  $86\% \pm 16\%$  (mean  $\pm$  SD) observed in adults. The mechanism for the diminished absolute bioavailability of lamivudine in infants and children is unknown.

Systemic clearance decreased with increasing age in pediatric patients, as shown in Figure 2.

**Figure 2. Systemic Clearance (L/hr\*kg) of Lamivudine in Relation to Age**



After oral administration of lamivudine 4 mg/kg twice daily to 11 pediatric patients ranging from 4 months to 14 years of age,  $C_{max}$  was  $1.1 \pm 0.6$  mcg/mL and half-life was  $2.0 \pm 0.6$  hours. (In adults

with similar blood sampling, the half-life was  $3.7 \pm 1$  hours.) Total exposure to lamivudine, as reflected by mean AUC values, was comparable between pediatric patients receiving an 8-mg/kg/day dose and adults receiving a 4-mg/kg/day dose.

Distribution of lamivudine into cerebrospinal fluid (CSF) was assessed in 38 pediatric patients after multiple oral dosing with lamivudine. CSF samples were collected between 2 and 4 hours postdose. At the dose of 8 mg/kg/day, CSF lamivudine concentrations in 8 patients ranged from 5.6% to 30.9% (mean  $\pm$  SD of  $14.2\% \pm 7.9\%$ ) of the concentration in a simultaneous serum sample, with CSF lamivudine concentrations ranging from 0.04 to 0.3 mcg/mL.

The effect of renal impairment on lamivudine pharmacokinetics in pediatric patients is not known.

The safety and pharmacokinetic properties of EPIVIR in combination with antiretroviral agents other than zidovudine have not been established in pediatric patients.

See INDICATIONS AND USAGE: Description of Clinical Studies, CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

**HBV:** See the complete prescribing information for EPIVIR-HBV Tablets and Oral Solution for additional information on the pharmacokinetics of lamivudine in HBV-infected children.

**Geriatric Use:** Clinical studies of EPIVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, because lamivudine is substantially excreted by the kidney and elderly patients are more likely to have decreased renal function, renal function should be monitored and dosage adjustments should be made accordingly (see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

## ADVERSE REACTIONS

**Clinical Trials in HIV: Adults:** Selected clinical adverse events with a  $\geq 5\%$  frequency during therapy with EPIVIR 150 mg twice daily plus RETROVIR 200 mg 3 times daily compared with zidovudine are listed in Table 5.



**Table 5. Selected Clinical Adverse Events (≥5% Frequency) in Four Controlled Clinical Trials (A3001, A3002, B3001, B3002)**

Adverse Event	EPIVIR 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR* (n = 230)
<b>Body as a whole</b>		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
<b>Digestive</b>		
Nausea	33%	29%
Diarrhea	18%	22%
Nausea & vomiting	13%	12%
Anorexia and/or decreased appetite	10%	7%
Abdominal pain	9%	11%
Abdominal cramps	6%	3%
Dyspepsia	5%	5%
<b>Nervous system</b>		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
<b>Respiratory</b>		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
<b>Skin</b>		
Skin rashes	9%	6%
<b>Musculoskeletal</b>		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

\*Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

The types and frequencies of clinical adverse events reported in patients receiving EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar. The most common adverse events in both treatment groups were nausea, dizziness, fatigue and/or malaise, headache, dreams, insomnia and other sleep disorders, and skin rash.

Pancreatitis was observed in 9 of the 2,613 adult patients (0.3%) who received EPIVIR in the controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and B3007.

Selected laboratory abnormalities observed during therapy are summarized in Table 6.

**Table 6. Frequencies of Selected Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Studies (A3001, A3002, B3001, B3002) and a Clinical Endpoint Study (B3007)**

Test (Threshold Level)	24-Week Surrogate Endpoint Studies*		Clinical Endpoint Study*	
	EPIVIR plus RETROVIR	Test RETROVIR <sup>†</sup>	EPIVIR plus Current Therapy	Placebo plus Current Therapy <sup>‡</sup>
Absolute neutrophil count ( $<750/\text{mm}^3$ )	7.2%	5.4%	15%	13%
Hemoglobin ( $<8.0$ g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets ( $<50,000/\text{mm}^3$ )	0.4%	1.3%	2.8%	3.8%
ALT ( $>5.0$ x ULN)	3.7%	3.6%	3.8%	1.9%
AST ( $>5.0$ x ULN)	1.7%	1.8%	4.0%	2.1%
Bilirubin ( $>2.5$ x ULN)	0.8%	0.4%	ND	ND
Amylase ( $>2.0$ x ULN)	4.2%	1.5%	2.2%	1.1%

\* The median duration on study was 12 months.

<sup>†</sup> Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

<sup>‡</sup> Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.

ULN = Upper limit of normal.

ND = Not done.

In small, uncontrolled studies in which pregnant women were given lamivudine alone or in combination with zidovudine beginning in the last few weeks of pregnancy (see PRECAUTIONS: Pregnancy), reported adverse events included anemia, urinary tract infections, and complications of labor and delivery. In postmarketing experience, liver function abnormalities and pancreatitis have been reported in women who received lamivudine in combination with other antiretroviral drugs during pregnancy. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared to other HIV-infected patients.

The frequencies of selected laboratory abnormalities reported in patients receiving EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination regimens in EPV20001 and

EPV40001) were similar.

**Pediatric Patients:** Selected clinical adverse events and physical findings with a  $\geq 5\%$  frequency during therapy with EPIVIR 4 mg/kg twice daily plus RETROVIR 160 mg/m<sup>2</sup> 3 times daily compared with didanosine in therapy-naive ( $\leq 56$  days of antiretroviral therapy) pediatric patients are listed in Table 7.

**Table 7. Selected Clinical Adverse Events and Physical Findings ( $\geq 5\%$  Frequency) in Pediatric Patients in Study ACTG300**

Adverse Event	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
<b>Body as a whole</b>		
Fever	25%	32%
<b>Digestive</b>		
Hepatomegaly	11%	11%
Nausea & vomiting	8%	7%
Diarrhea	8%	6%
Stomatitis	6%	12%
Splenomegaly	5%	8%
<b>Respiratory</b>		
Cough	15%	18%
Abnormal breath sounds/wheezing	7%	9%
<b>Ear, Nose, and Throat</b>		
Signs or symptoms of ears*	7%	6%
Nasal discharge or congestion	8%	11%
<b>Other</b>		
Skin rashes	12%	14%
Lymphadenopathy	9%	11%

\*Includes pain, discharge, erythema, or swelling of an ear.

Selected laboratory abnormalities experienced by therapy-naive ( $\leq 56$  days of antiretroviral therapy) pediatric patients are listed in Table 8.

**Table 8. Frequencies of Selected Laboratory Abnormalities in Pediatric Patients in Study ACTG300**

Test (Threshold Level)	EPIVIR plus RETROVIR	Didanosine
Absolute neutrophil count (<400/mm <sup>3</sup> )	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm <sup>3</sup> )	1%	3%
ALT (>10 x ULN)	1%	3%
AST (>10 x ULN)	2%	4%
Lipase (>2.5 x ULN)	3%	3%
Total Amylase (>2.5 x ULN)	3%	3%

ULN = Upper limit of normal.

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric patients receiving EPIVIR alone or in combination with other antiretroviral agents. In an open-label dose-escalation study (A2002), 14 patients (14%) developed pancreatitis while receiving monotherapy with EPIVIR. Three of these patients died of complications of pancreatitis. In a second open-label study (A2005), 12 patients (18%) developed pancreatitis. In Study ACTG300, pancreatitis was not observed in 236 patients randomized to EPIVIR plus RETROVIR. Pancreatitis was observed in 1 patient in this study who received open-label EPIVIR in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy.

Paresthesias and peripheral neuropathies were reported in 15 patients (15%) in Study A2002, 6 patients (9%) in Study A2005, and 2 patients (<1%) in Study ACTG300.

Limited short-term safety information is available from 2 small, uncontrolled studies in South Africa in neonates receiving lamivudine with or without zidovudine for the first week of life following maternal treatment starting at week 38 or 36 of gestation (see PRECAUTIONS: Pediatric Use). Adverse events reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis, and syphilis; 3 neonates died (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes). Two other nonfatal gastroenteritis or diarrhea cases were reported, including 1 with convulsions; 1 infant had transient renal insufficiency associated with dehydration.

The absence of control groups further limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse events comparable to those reported in pediatric and adult HIV-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

**Lamivudine in Patients with Chronic Hepatitis B:** Clinical trials in chronic hepatitis B used a lower dose of lamivudine (100 mg daily) than the dose used to treat HIV. The most frequent adverse events with lamivudine versus placebo were ear, nose, and throat infections (25% versus 21%); malaise and fatigue (24% versus 28%); and headache (21% versus 21%), respectively. The most frequent laboratory abnormalities reported with lamivudine were elevated ALT, elevated serum lipase, elevated CPK, and posttreatment elevations of liver function tests. Emergence of HBV viral mutants during lamivudine treatment, associated with reduced drug susceptibility and diminished treatment response, was also reported (also see WARNINGS and PRECAUTIONS). Please see the complete prescribing information for EPIVIR-HBV Tablets and Oral Solution for more information.

**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of lamivudine. 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.

**Body as a Whole:** Redistribution/accumulation of body fat (see PRECAUTIONS: Fat Redistribution).

**Digestive:** Stomatitis.

**Endocrine and Metabolic:** Hyperglycemia.

**General:** Weakness.

**Hemic and Lymphatic:** Anemia (including pure red cell aplasia and severe anemias progressing on therapy), lymphadenopathy, splenomegaly.

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

**Hypersensitivity:** Anaphylaxis, urticaria.

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

**Nervous:** Paresthesia, peripheral neuropathy.

**Respiratory:** Abnormal breath sounds/wheezing.

**Skin:** Alopecia, rash, pruritus.

## OVERDOSAGE

There is no known antidote for EPIVIR. One case of an adult ingesting 6 g of EPIVIR was reported; there were no clinical signs or symptoms noted and hematologic tests remained normal. Two cases of pediatric overdose were reported in ACTG300. One case was a single dose of 7 mg/kg of EPIVIR; the second case involved use of 5 mg/kg of EPIVIR twice daily for 30 days. There were no clinical signs or symptoms noted in either case. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.

## DOSAGE AND ADMINISTRATION

**Adults:** The recommended oral dose of EPIVIR for adults is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents (see DESCRIPTION OF CLINICAL STUDIES, PRECAUTIONS, MICROBIOLOGY, and CLINICAL PHARMACOLOGY). If lamivudine is administered to a patient dually infected with HIV and HBV, the dosage indicated for HIV therapy should be used as part of an appropriate combination regimen (see WARNINGS).

**Pediatric Patients *Infants/Children/Adolescents*:** The recommended oral dose of EPIVIR for HIV-infected pediatric patients 3 months up to 16 years of age is 4 mg/kg twice daily (up to a maximum of 150 mg twice a day), administered in combination with other antiretroviral agents.

**Dose Adjustment:** It is recommended that doses of EPIVIR be adjusted in accordance with renal function (see Table 9) (see CLINICAL PHARMACOLOGY).

**Table 9. Adjustment of Dosage of EPIVIR in Adults and Adolescents in Accordance with Creatinine Clearance**

Creatinine Clearance (mL/min)	Recommended Dosage of EPIVIR
≥50	150 mg twice daily or 300 mg once 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

Insufficient data are available to recommend a dosage of EPIVIR in patients undergoing dialysis. Although there are insufficient data to recommend a specific dose adjustment of EPIVIR in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered.

## HOW SUPPLIED

EPIVIR Tablets, 150 mg, are white, modified diamond-shaped, film-coated tablets engraved with "150" on one side and "GX CJ7" on the reverse side.

Bottle of 60 tablets (NDC 0173-0470-01) with child-resistant closure.

EPIVIR Tablets, 300 mg, are gray, modified diamond-shaped, film-coated tablets engraved with "GX EJ7" on one side and plain on the reverse side.

Bottle of 30 tablets (NDC 0173-0714-00) with child-resistant closure.

**Store at 25°C (77°F), excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].**

EPIVIR Oral Solution, a clear, colorless to pale yellow, strawberry-banana flavored liquid, contains 10 mg of lamivudine in each 1 mL in plastic bottles of 240 mL (NDC 0173-0471-00) with child-resistant closures. This product does not require reconstitution.

**Store in tightly closed bottles at 25°C (77°F) [see USP Controlled Room Temperature].**



GlaxoSmithKline

Research Triangle Park, NC 27709

Manufactured under agreement from

**Shire Pharmaceuticals Group plc**

Basingstoke, UK

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Date of Issue

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/s/

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Debra Birnkrant  
10/8/02 12:55:35 PM  
NDA 20-596, NDA 20-564

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FUZEON safely and effectively. See full prescribing information for FUZEON.

FUZEON® (enfuvirtide) for Injection  
Initial U.S. Approval: 2003

### RECENT MAJOR CHANGES

Warnings and Precautions, Pneumonia (5.3) 04/2011

### INDICATIONS AND USAGE

FUZEON is an HIV-1 fusion inhibitor indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with HIV-1 replication despite ongoing antiretroviral therapy. (1)

### DOSAGE AND ADMINISTRATION

- Adults: Recommended FUZEON dose of 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen. FUZEON should not be injected near any anatomical areas where large nerves course close to the skin. (2.1)
- Pediatric Patients (6 to 16 years of age): Recommended 2 mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously. Weight should be monitored periodically and the FUZEON dose should be adjusted accordingly. (2.2)
- FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection provided in the Convenience Kit. (2.3)
- Reconstituted FUZEON must be injected immediately or kept refrigerated in the original vial. It must be used within 24 hours. (2.3)

### DOSAGE FORMS AND STRENGTHS

- Lyophilized powder: 108 mg/vial (3)

### CONTRAINDICATIONS

- Hypersensitivity to FUZEON or any of its components. (4)

### WARNINGS AND PRECAUTIONS

- Injection Site Reaction: 98% of subjects experienced at least one injection site reaction during FUZEON treatment in randomized, controlled, open-label, multicenter trials. Manifestations included pain and discomfort, erythema, nodules and cysts, and ecchymosis. (5.1)

- Biojector® 2000: Administration of FUZEON with Biojector 2000 may result in neuralgia and/or paresthesia, bruising and hematomas. Patients receiving anticoagulants or persons with hemophilia, or other coagulation disorders, may have a higher risk of post-injection bleeding. (5.2)
- Pneumonia: Monitor for signs and symptoms of pneumonia in HIV-infected patients, especially those predisposed to pneumonia (e.g., low initial CD4 cell count). (5.3)
- Hypersensitivity: FUZEON should be discontinued immediately upon signs and symptoms of systemic hypersensitivity reactions. (5.4)
- Immune Reconstitution: Patients treated with combination antiretroviral therapy, including FUZEON, may experience immune reconstitution syndrome requiring further evaluation and treatment. (5.6)

### ADVERSE REACTIONS

Most common adverse reactions are local injection site reactions, diarrhea, nausea, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- No dose adjustments of FUZEON or the co-administered drug is needed when FUZEON is administered concomitantly with other antiretroviral or non-antiretroviral drugs. (7, 12.3)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: No evidence of harm to the fetus was observed in animal reproduction studies and FUZEON should be used only if clearly needed. (8.1)
- Nursing mothers: Do not breast-feed while receiving FUZEON therapy. (8.3)
- Pediatric Use: Safety and pharmacokinetics of FUZEON have not been established in pediatric patients < 6 years of age. Limited efficacy data for pediatric patients ≥ 6 years of age. (8.4)
- Geriatric Use: No data available for patients ≥ 65 years of age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2011

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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

FUZEON® in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

This indication is based on results from two controlled studies of 48 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of FUZEON in antiretroviral naive subjects.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Adults

The recommended dose of FUZEON is 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site, and only where there is no current injection site reaction from an earlier dose. FUZEON should not be injected near any anatomical areas where large nerves course close to the skin, such as near the elbow, knee, groin or the inferior or medial section of the buttocks, skin abnormalities, including directly over a blood vessel, into moles, scar tissue, bruises, or near the navel, surgical scars, tattoos or burn sites. Additional detailed information regarding the administration of FUZEON is described in the *FUZEON Injection Instructions*.

#### 2.2 Pediatric Patients

Insufficient data are available to establish a dose recommendation of FUZEON in pediatric patients below the age of 6 years. In pediatric patients 6 years through 16 years of age, the recommended dosage of FUZEON is 2 mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction from an earlier dose. FUZEON should not be injected into moles, scar tissue, bruises or the navel. Table 1 contains dosing guidelines for FUZEON based on body weight. Weight should be monitored periodically and the FUZEON dose adjusted accordingly.

**Table 1 Pediatric Dosing Guidelines**

Weight		Dose per bid Injection (mg/dose)	Injection Volume (90 mg enfuvirtide per mL)
Kilograms (kg)	Pounds (lbs)		
11.0 to 15.5	24 to 34	27	0.3 mL
15.6 to 20.0	>34 to 44	36	0.4 mL
20.1 to 24.5	>44 to 54	45	0.5 mL
24.6 to 29.0	>54 to 64	54	0.6 mL
29.1 to 33.5	>64 to 74	63	0.7 mL
33.6 to 38.0	>74 to 84	72	0.8 mL
38.1 to 42.5	>84 to 94	81	0.9 mL
≥42.6	>94	90	1.0 mL

#### 2.3 Directions for Use

For more detailed instructions, see *FUZEON Injection Instructions*.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

#### Subcutaneous Administration

FUZEON must only be reconstituted with 1.1 mL of Sterile Water for Injection provided in the Convenience Kit. After adding sterile water, the vial should be gently tapped for 10 seconds and then gently rolled between the hands to avoid foaming and to ensure all particles of drug are in contact with the liquid and no drug remains

on the vial wall. The vial should then be allowed to stand until the powder goes completely into solution, which could take up to 45 minutes. Reconstitution time can be reduced by gently rolling the vial between the hands until the product is completely dissolved. Before the solution is withdrawn for administration, the vial should be inspected visually to ensure that the contents are fully dissolved in solution, and that the solution is clear, colorless and without bubbles or particulate matter. If the FUZEON is foamy or jelled, allow more time for it to dissolve. If there is evidence of particulate matter, the vial must not be used and should be returned to the pharmacy.

FUZEON contains no preservatives. Once reconstituted, FUZEON should be injected immediately or kept refrigerated in the original vial until use. Reconstituted FUZEON must be used within 24 hours. The subsequent dose of FUZEON can be reconstituted in advance and must be stored in the refrigerator in the original vial and used within 24 hours. Refrigerated reconstituted solution should be brought to room temperature before injection and the vial should be inspected visually again to ensure that the contents are fully dissolved in solution and that the solution is clear, colorless, and without bubbles or particulate matter.

A vial is suitable for single use only; unused portions must be discarded (see FUZEON *Injection Instructions*).

Patients should contact their healthcare provider for any questions regarding the administration of FUZEON. Information about the self-administration of FUZEON may also be obtained by calling the toll-free number 1-877-4-FUZEON (1-877-438-9366) or at the FUZEON website, [www.FUZEON.com](http://www.FUZEON.com). Patients should be taught to recognize the signs and symptoms of injection site reactions and instructed when to contact their healthcare provider about these reactions.

### **3 DOSAGE FORMS AND STRENGTHS**

Lyophilized powder for injection: 108 mg enfuvirtide per vial

### **4 CONTRAINDICATIONS**

FUZEON is contraindicated in patients with known hypersensitivity to FUZEON or any of its components [see *Warnings and Precautions (5.4)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Local Injection Site Reactions (ISRs)**

The majority of subjects (98%) receiving FUZEON in randomized, controlled, open-label, multicenter clinical trials had at least one local injection site reaction; ISRs occurred throughout treatment with FUZEON. Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis [see *Adverse Reactions (6)*]. Reactions are often present at more than one injection site. Patients must be familiar with the FUZEON *Injection Instructions* in order to know how to inject FUZEON appropriately and how to monitor carefully for signs or symptoms of cellulitis or local infection.

#### **5.2 Administration with Biojector® 2000**

Nerve pain (neuralgia and/or paresthesia) lasting up to 6 months associated with administration at anatomical sites where large nerves course close to the skin, bruising and hematomas have occurred with use of the Biojector 2000 needle-free device for administration of FUZEON. Patients receiving anticoagulants or persons with hemophilia, or other coagulation disorders, may have a higher risk of post-injection bleeding.

#### **5.3 Pneumonia**

An increased rate of bacterial pneumonia was observed in subjects treated with FUZEON in the Phase 3 clinical trials compared to the control arm. The incidence of pneumonia was 2.7% or 3.2 events/100 patient-years in subjects receiving FUZEON+background regimen. On analysis of all diagnoses of pneumonia (pneumonia, bacterial pneumonia, bronchopneumonia, and related terms) in T20-301 and T20-302, an increased rate of bacterial pneumonia was observed in subjects treated with FUZEON compared to the control arm (6.9%, 6.7 pneumonia events per 100 patient-years versus 0.6 events per 100 patient-years, respectively). Approximately half of the study subjects with pneumonia required hospitalization. Three subject deaths in the FUZEON arm