HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EPIVIR (lamivudine) tablets for oral use
EPIVIR (lamivudine) oral solution
Initial U.S. Approval: 1995

WARNING: LACTIC ACIDOSIS, POSTTREATMENT EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS, DIFFERENT FORMULATIONS OF EPIVIR

See full prescribing information for complete boxed warning

- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)**
- **Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued EPIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)**
- **Patients with HIV-1 infection should receive only dosage forms of EPIVIR appropriate for treatment of HIV-1. (5.2)**

RECENT MAJOR CHANGES

Dosage and Administration (2.2) 03/2015

INDICATIONS AND USAGE

EPIVIR is a nucleoside analogue reverse transcriptase inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Limitation of Use: The dosage of this product is for HIV-1 and not for HBV. (1)

DOSAGE AND ADMINISTRATION

- Adults: 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily. (2.1)
- Pediatric Patients Aged 3 Months and Older: Administered either once or twice daily. Dose should be calculated on body weight (kg) and should not exceed 300 mg daily. (2.2)
- Patients with Renal Impairment: Doses of EPIVIR must be adjusted in accordance with renal function. (2.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 300 mg (3)
- Tablets: 150 mg scored (3)
- Oral Solution: 10 mg per mL (3)

CONTRAINDICATIONS

EPIVIR tablets and oral solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products. (4)

WARNINGS AND PRECAUTIONS

- Lactic acidosis and severe hepatomegaly with steatosis: Reported with the use of nucleoside analogues. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.1)
- Severe acute exacerbations of hepatitis: Reported in patients who are co-infected with hepatitis B virus and HIV-1 and discontinued EPIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.2)
- Patients with HIV-1 infection should receive only dosage forms of EPIVIR appropriate for treatment of HIV-1. (5.2)
- Co-infected HIV-1/HBV Patients: Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. (5.2)
- Emtricitabine should not be administered concomitantly with lamivudine-containing products. (5.3)
- Hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving interferon and ribavirin-based regimens. Monitor for treatment-associated toxicities. Discontinue EPIVIR as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.5)
- Immune reconstitution syndrome (5.6) and redistribution/accumulation of body fat (5.7) have been reported in patients treated with combination antiretroviral therapy.

ADVERSE REACTIONS

- The most common reported adverse reactions (incidence greater than or equal to 15%) in adults were headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea, and cough. (6.1)
- The most common reported adverse reactions (incidence greater than or equal to 15%) in pediatric subjects were fever and cough. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Zalcitabine is not recommended for use in combination with EPIVIR. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding not recommended. (8.2)

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

Revised: 03/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS, POSTTREATMENT EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS, DIFFERENT FORMULATIONS OF EPIVIR®.

Lactic Acidosis and Severe Hepatomegaly

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. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.1)]*.

Exacerbations of Hepatitis B

Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued EPIVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue EPIVIR and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.2)]*.

Important Differences among Lamivudine-containing Products

EPIVIR tablets and oral solution (used to treat HIV-1 infection) contain a higher dose of the active ingredient (lamivudine) than EPIVIR-HBV® tablets and oral solution (used to treat chronic HBV infection). Patients with HIV-1 infection should receive only dosage forms appropriate for treatment of HIV-1 *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

EPIVIR is a nucleoside analogue indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection. Limitation of use: The dosage of this product is for HIV-1 and not for HBV.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

- The recommended oral dose of EPIVIR in HIV-1-infected adults is 300 mg daily, administered as either 150 mg twice daily or 300 mg once daily, in combination with other antiretroviral agents. If lamivudine is administered to a patient infected with HIV-1 and HBV, the dosage indicated for HIV-1 therapy should be used as part of an appropriate combination regimen *[see Warnings and Precautions (5.2)]*.
- EPIVIR may be taken with or without food.

2.2 Pediatric Patients

The recommended oral dose of EPIVIR oral solution in HIV-1-infected pediatric patients aged 3 months and older is 4 mg per kg twice daily or 8 mg per kg once daily (up to a maximum of 300 mg daily), administered in combination with other antiretroviral agents. Consider HIV-1 viral load and CD4+ cell count/percentage when selecting the dosing interval for patients initiating treatment with oral solution *[see Clinical Pharmacology (12.3)]*.

EPIVIR is also available as a scored tablet for HIV-1-infected pediatric patients who weigh at least 14 kg and for whom a solid dosage form is appropriate. Before prescribing EPIVIR tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow EPIVIR tablets, the oral solution formulation should be prescribed. The recommended oral dosage of EPIVIR tablets for HIV-1-infected pediatric patients is presented in Table 1.

Table 1. Dosing Recommendations for EPIVIR Scored (150-mg) Tablets in Pediatric Patients

Weight (kg)	Once-daily Dosing Regimen[a]	Twice-daily Dosing Regimen Using Scored 150-mg Tablet		
		AM Dose	PM Dose	Total Daily Dose
14 to <20	1 tablet (150 mg)	½ tablet (75 mg)	½ tablet (75 mg)	150 mg
≥20 to <25	1½ tablets (225 mg)	½ tablet (75 mg)	1 tablet (150 mg)	225 mg
≥25	2 tablets (300 mg)[b]	1 tablet (150 mg)	1 tablet (150 mg)	300 mg

[a] Data regarding the efficacy of once-daily dosing is limited to subjects who transitioned from twice-daily dosing to once-daily dosing after 36 weeks of treatment *[see Clinical Studies (14.2)]*.

[b] Patients may alternatively take one 300-mg tablet, which is not scored.

2.3 Patients with Renal Impairment

Dosing of EPIVIR is adjusted in accordance with renal function. Dosage adjustments are listed in Table 2 *[see Clinical Pharmacology (12.3)]*.

Table 2. Adjustment of Dosage of EPIVIR in Adults and Adolescents (Greater than or Equal to 25 kg) 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

No additional dosing of EPIVIR is required after routine (4-hour) hemodialysis or peritoneal 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.

3 DOSAGE FORMS AND STRENGTHS

- **EPIVIR Scored Tablets**

150 mg, are white, diamond-shaped, scored, film-coated tablets debossed with “GX CJ7” on both sides.

- **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.

- **EPIVIR Oral Solution**

A clear, colorless to pale yellow, strawberry-banana flavored liquid, containing 10 mg of lamivudine per 1 mL.

4 CONTRAINDICATIONS

EPIVIR tablets and oral solution are contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., anaphylaxis) to any of the components of the products.

5 WARNINGS AND PRECAUTIONS

5.1 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 also have 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).

5.2 Patients with HIV-1 and Hepatitis B Virus Co-infection

Posttreatment Exacerbations of Hepatitis

In clinical trials in non-HIV-1-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 postmarketing experience after changes from lamivudine-containing HIV-1 treatment regimens to non-lamivudine-containing regimens in patients infected with both HIV-1 and HBV. The causal relationship to discontinuation of lamivudine treatment is unknown. Patients should be closely monitored with both clinical and laboratory follow-up 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.

Important Differences among Lamivudine-containing Products

EPIVIR tablets and oral solution contain a higher dose of the same active ingredient (lamivudine) than EPIVIR-HBV tablets and EPIVIR-HBV 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 co-infected with HIV-1 and HBV. Safety and efficacy of lamivudine have not been established for treatment of chronic hepatitis B in patients co-infected with HIV-1 and HBV. If treatment with EPIVIR-HBV is prescribed for chronic hepatitis B for a patient with unrecognized or untreated HIV-1 infection, rapid emergence of HIV-1 resistance is likely to result because of the subtherapeutic dose and the inappropriateness of monotherapy HIV-1 treatment. If a decision is made to administer lamivudine to patients co-infected with HIV-1 and HBV, EPIVIR tablets, EPIVIR oral solution, or another product containing the higher dose of lamivudine should be used as part of an appropriate combination regimen.

Emergence of Lamivudine-resistant HBV

In non–HIV-1-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 full prescribing information for EPIVIR-HBV for additional information). Emergence of hepatitis B virus variants associated with resistance to lamivudine has also been

reported in HIV-1-infected patients who have received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus.

5.3 Use with Other Lamivudine- and Emtricitabine-containing Products

EPIVIR is one of multiple lamivudine-containing products. Concomitant administration of EPIVIR with other products containing lamivudine is not recommended. Concomitant use of EPIVIR with emtricitabine-containing products is also not recommended.

5.4 Use with Interferon- and Ribavirin-based Regimens

In vitro studies have shown ribavirin can reduce the phosphorylation of pyrimidine nucleoside analogues such as lamivudine. Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients *[see Clinical Pharmacology (12.3)]*, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin. Patients receiving interferon alfa with or without ribavirin and EPIVIR should be closely monitored for treatment-associated toxicities, especially hepatic decompensation. Discontinuation of EPIVIR should be considered as medically appropriate. Dose reduction or discontinuation of interferon alfa, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6). See the complete prescribing information for interferon and ribavirin.

5.5 Pancreatitis

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 (6.1)]*.

5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including EPIVIR. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.7 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Lactic acidosis and severe hepatomegaly with steatosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.
- Severe acute exacerbations of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C *[see Warnings and Precautions (5.4)]*.
- Pancreatitis *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Trials Experience in Adult Subjects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of EPIVIR in adults is primarily based on 3,568 HIV-1-infected subjects in 7 clinical trials.

The most common adverse reactions are headache, nausea, malaise, fatigue, nasal signs and symptoms, diarrhea and cough.

Selected clinical adverse reactions in greater than or equal to 5% of subjects during therapy with EPIVIR 150 mg twice daily plus RETROVIR® 200 mg 3 times daily for up to 24 weeks are listed in Table 3.

Table 3. Selected Clinical Adverse Reactions (Greater than or Equal to 5% Frequency) in Four Controlled Clinical Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002)

Adverse Reaction	EPIVIR 150 mg Twice Daily plus RETROVIR (n = 251)	RETROVIR[a] (n = 230)
Body as a Whole		
Headache	35%	27%
Malaise & fatigue	27%	23%
Fever or chills	10%	12%
Digestive		
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%
Nervous System		
Neuropathy	12%	10%
Insomnia & other sleep disorders	11%	7%
Dizziness	10%	4%
Depressive disorders	9%	4%
Respiratory		
Nasal signs & symptoms	20%	11%
Cough	18%	13%
Skin		
Skin rashes	9%	6%
Musculoskeletal		
Musculoskeletal pain	12%	10%
Myalgia	8%	6%
Arthralgia	5%	5%

[a] Either zidovudine monotherapy or zidovudine in combination with zalcitabine.

Pancreatitis: Pancreatitis was observed in 9 out of 2,613 adult subjects (0.3%) who received EPIVIR in controlled clinical trials EPV20001, NUCA3001, NUCB3001, NUCA3002, NUCB3002, and NUCB3007 *[see Warnings and Precautions (5.5)]*.

EPIVIR 300 mg Once Daily: The types and frequencies of clinical adverse reactions reported in subjects receiving EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) for 48 weeks were similar.

Selected laboratory abnormalities observed during therapy are summarized in Table 4.

Table 4. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Adults in Four 24-Week Surrogate Endpoint Trials (NUCA3001, NUCA3002, NUCB3001, NUCB3002) and a Clinical Endpoint Trial (NUCB3007)

	24-Week Surrogate Endpoint Trials[a]		Clinical Endpoint Trial[a]	
Test (Threshold Level)	EPIVIR plus RETROVIR	RETROVIR[b]	EPIVIR plus Current Therapy[c]	Placebo plus Current Therapy[c]
Absolute neutrophil count (<750/mm^3)	7.2%	5.4%	15%	13%
Hemoglobin (<8.0 g/dL)	2.9%	1.8%	2.2%	3.4%
Platelets (<50,000/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%

[a] The median duration on study was 12 months.
[b] Either zidovudine monotherapy or zidovudine in combination with zalcitabine.
[c] Current therapy was either zidovudine, zidovudine plus didanosine, or zidovudine plus zalcitabine.
ULN = Upper limit of normal.
ND = Not done.

The frequencies of selected laboratory abnormalities reported in subjects receiving EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily (in 3-drug combination regimens in EPV20001 and EPV40001) were similar.

6.2 Clinical Trials Experience in Pediatric Subjects

EPIVIR oral solution has been studied in 638 pediatric subjects aged 3 months to 18 years in 3 clinical trials.

Selected clinical adverse reactions and physical findings with a greater than or equal to 5% frequency during therapy with EPIVIR 4 mg per kg twice daily plus RETROVIR 160 mg per m^2 3 times daily in therapy-naive (less than or equal to 56 days of antiretroviral therapy) pediatric subjects are listed in Table 5.

Table 5. Selected Clinical Adverse Reactions and Physical Findings (Greater than or Equal to 5% Frequency) in Pediatric Subjects in Trial ACTG300

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

[a] Includes pain, discharge, erythema, or swelling of an ear.

Pancreatitis

Pancreatitis, which has been fatal in some cases, has been observed in antiretroviral nucleoside-experienced pediatric subjects receiving EPIVIR alone or in combination with other antiretroviral agents. In an open-label dose-escalation trial (NUCA2002), 14 subjects (14%) developed pancreatitis while receiving monotherapy with EPIVIR. Three of these subjects died of complications of pancreatitis. In a second open-label trial (NUCA2005), 12 subjects (18%) developed pancreatitis. In Trial ACTG300, pancreatitis was not observed in 236 subjects randomized to EPIVIR plus RETROVIR. Pancreatitis was observed in 1 subject in this trial who received open-label EPIVIR in combination with RETROVIR and ritonavir following discontinuation of didanosine monotherapy *[see Warnings and Precautions (5.5)]*.

Paresthesias and Peripheral Neuropathies

Paresthesias and peripheral neuropathies were reported in 15 subjects (15%) in Trial NUCA2002, 6 subjects (9%) in Trial NUCA2005, and 2 subjects (less than 1%) in Trial ACTG300.

Selected laboratory abnormalities experienced by therapy-naive (less than or equal to 56 days of

antiretroviral therapy) pediatric subjects are listed in Table 6.

Table 6. Frequencies of Selected Grade 3-4 Laboratory Abnormalities in Pediatric Subjects in Trial ACTG300

Test (Threshold Level)	EPIVIR plus RETROVIR	Didanosine
Absolute neutrophil count (<400/mm^3)	8%	3%
Hemoglobin (<7.0 g/dL)	4%	2%
Platelets (<50,000/mm^3)	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.

Pediatric Subjects Once-daily vs Twice-daily Dosing (COL105677)

The safety of once-daily compared with twice-daily dosing of EPIVIR was assessed in the ARROW trial. Primary safety assessment in the ARROW trial was based on Grade 3 and Grade 4 adverse events. The frequency of Grade 3 and 4 adverse events was similar among subjects randomized to once-daily dosing compared with subjects randomized to twice-daily dosing. One event of Grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other Grade 3 or 4 adverse events were considered not related by the investigator.

Neonates

Limited short-term safety information is available from 2 small, uncontrolled trials 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 Clinical Pharmacology (12.3)]*. Selected adverse reactions reported in these neonates included increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, and sepsis; 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 limits assessments of causality, but it should be assumed that perinatally exposed infants may be at risk for adverse reactions comparable to those reported in pediatric and adult HIV-1-infected patients treated with lamivudine-containing combination regimens. Long-term effects of in utero and infant lamivudine exposure are not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of EPIVIR.

Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions 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 Warnings and Precautions (5.7)]*.

Endocrine and Metabolic

Hyperglycemia.

General

Weakness.

Hemic and Lymphatic

Anemia (including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic

Lactic acidosis and hepatic steatosis, posttreatment exacerbation of hepatitis B *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*.

Hypersensitivity

Anaphylaxis, urticaria.

Musculoskeletal

Muscle weakness, CPK elevation, rhabdomyolysis.

Skin

Alopecia, pruritus.

7 DRUG INTERACTIONS

Lamivudine is predominantly eliminated in the urine by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system (e.g., trimethoprim). No data are available regarding interactions with other drugs that have renal clearance mechanisms similar to that of lamivudine.

7.1 Interferon- and Ribavirin-based Regimens

Although no evidence of a pharmacokinetic or pharmacodynamic interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when ribavirin was coadministered with lamivudine in HIV-1/HCV co-infected patients, hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for

HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

7.2 Zalcitabine

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

7.3 Trimethoprim/Sulfamethoxazole (TMP/SMX)

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 PCP.

7.4 Drugs with No Observed Interactions with EPIVIR

A drug interaction trial showed no clinically significant interaction between EPIVIR and zidovudine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to EPIVIR during pregnancy. Physicians are encouraged to register patients by calling the Antiretroviral Pregnancy Registry at 1-800-258-4263.

Risk Summary

Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for lamivudine compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Lamivudine produced embryonic toxicity in rabbits at a dose that produced similar human exposures as the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.

Data

Human Data: Based on prospective reports from the Antiretroviral Pregnancy Registry of over 11,000 exposures to lamivudine during pregnancy resulting in live births (including over 4,300 exposed in the first trimester), there was no difference between lamivudine and overall birth defects compared with the background birth defect rate of 2.7% in the US reference population of the MACDP. The prevalence of defects in the first trimester was 3.1% (95% CI: 2.6% to 3.7%).

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks gestation using 150 mg lamivudine twice daily with zidovudine, 10 women at 38 weeks gestation using 150 mg

lamivudine twice daily with zidovudine, and 10 women at 38 weeks gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine pharmacokinetics in pregnant women were similar to those seen in non-pregnant adults and in postpartum women. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels and ranged from 1.2 to 2.5 mcg per mL (150 mg twice daily) and 2.1 to 5.2 mcg per mL (300 mg twice daily).

Animal Data: Studies in pregnant rats 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 producing plasma levels up to approximately 35 times that for the recommended adult HIV dose. No evidence of teratogenicity due to lamivudine was observed. Evidence of embryo-lethality 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 those in humans.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Because of the potential for HIV-1 transmission mothers should be instructed not to breastfeed.

8.4 Pediatric Use

The safety and effectiveness of EPIVIR in combination with other antiretroviral agents have been established in pediatric patients aged 3 months and older *[see Dosage and Administration (2.2), Adverse Reactions (6.2), Clinical Pharmacology (12.3), Clinical Studies (14.2)]*.

8.5 Geriatric Use

Clinical trials 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 Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

8.6 Patients with Impaired Renal Function

Reduction of the dosage of EPIVIR is recommended for patients with impaired renal function

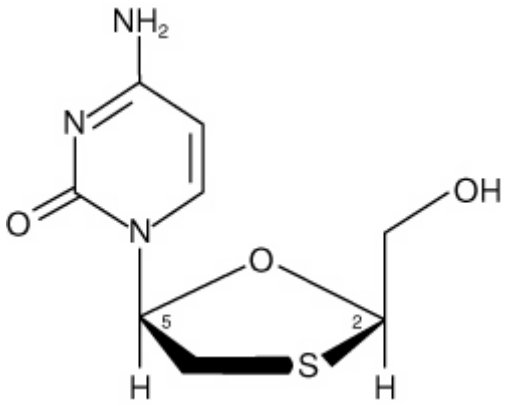
[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].

10 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 Trial ACTG300. One case involved a single dose of 7 mg per kg of EPIVIR; the second case involved use of 5 mg per kg of EPIVIR twice daily for 30 days. There were no clinical signs or symptoms noted in either case. Because a negligible amount of lamivudine was removed via (4-hour) hemodialysis, continuous ambulatory peritoneal dialysis, and automated peritoneal dialysis, it is not known if continuous hemodialysis would provide clinical benefit in a lamivudine overdose event. If overdose occurs, the patient should be monitored, and standard supportive treatment applied as required.

11 DESCRIPTION

EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg per mL in water at 20°C.

EPIVIR tablets are for oral administration. Each scored 150-mg film-coated tablet contains 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene

glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

EPIVIR oral solution is for oral administration. One milliliter (1 mL) of EPIVIR oral solution contains 10 mg of lamivudine (10 mg per mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lamivudine is an antiviral agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-1-infected adult subjects after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg per kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg per kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg per day administered to HBV-infected subjects.

The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for 7 days compared with the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a crossover trial in 60 healthy subjects. EPIVIR 300 mg once daily resulted in lamivudine exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared with the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared with the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-1-infected subjects. Absolute bioavailability in 12 adult subjects was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg per kg twice a day to 9 adults with HIV-1, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg per mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg per kg.

The accumulation ratio of lamivudine in HIV-1-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg per kg twice daily.

Effects of Food on Oral Absorption: An investigational 25-mg dosage form of

lamivudine was administered orally to 12 asymptomatic, HIV-1-infected subjects on 2 occasions, once in the fasted state and once with food (1,099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours); C_{max} in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC∞) in the fed and fasted states; therefore, EPIVIR tablets and oral solution may be administered with or without food.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 subjects was 1.3 ± 0.4 L per kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (less than 36%). In vitro studies showed that over the concentration range of 0.1 to 100 mcg per mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.

Metabolism: Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in 6 HIV-1-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.

Elimination: The majority of lamivudine is eliminated unchanged in urine by active organic cationic secretion. In 9 healthy subjects given a single 300-mg oral dose of lamivudine, renal clearance was 199.7 ± 56.9 mL per min (mean ± SD). In 20 HIV-1-infected subjects given a single IV dose, renal clearance was 280.4 ± 75.2 mL per min (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.

In most single-dose trials in HIV-1-infected subjects, HBV-infected subjects, or healthy subjects with serum sampling for 24 hours after dosing, the observed mean elimination half-life ($t_{½}$) ranged from 5 to 7 hours. In HIV-1-infected subjects, total clearance was 398.5 ± 69.1 mL per min (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range of 0.25 to 10 mg per kg.

Special Populations

Renal Impairment: The pharmacokinetic properties of lamivudine have been determined in a small group of HIV-1-infected adults with impaired renal function (Table 7).

Table 7. Pharmacokinetic Parameters (Mean ± SD) after a Single 300-mg Oral Dose of Lamivudine in 3 Groups of Adults with Varying Degrees of Renal Function

Parameter	Creatinine Clearance Criterion (Number of Subjects)		
	>60 mL/min (n = 6)	10-30 mL/min (n = 4)	<10 mL/min (n = 6)
Creatinine clearance (mL/min)	111 ± 14	28 ± 8	6 ± 2
C_{max} (mcg/mL)	2.6 ± 0.5	3.6 ± 0.8	5.8 ± 1.2
AUC∞ (mcg•h/mL)	11.0 ± 1.7	48.0 ± 19	157 ± 74
Cl/F (mL/min)	464 ± 76	114 ± 34	36 ± 11

Exposure (AUC∞), C_{max}, and half-life increased with diminishing renal function (as expressed by creatinine clearance). Apparent total oral clearance (Cl/F) of lamivudine decreased as creatinine clearance decreased. T_{max} was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of lamivudine be modified in patients with renal impairment *[see Dosage and Administration (2.3)]*.

Based on a trial in otherwise healthy subjects with impaired renal function, hemodialysis increased lamivudine clearance from a mean of 64 to 88 mL per min; however, the length of time of hemodialysis (4 hours) was insufficient to significantly alter mean lamivudine exposure after a single-dose administration. Continuous ambulatory peritoneal dialysis and automated peritoneal dialysis have negligible effects on lamivudine clearance. Therefore, it is recommended, following correction of dose for creatinine clearance, that no additional dose modification be made after routine hemodialysis or peritoneal dialysis.

It is not known whether lamivudine can be removed by continuous (24-hour) hemodialysis.

The effects of renal impairment on lamivudine pharmacokinetics in pediatric patients are not known.

Hepatic Impairment: The pharmacokinetic properties of lamivudine have been determined in adults with impaired hepatic function. Pharmacokinetic parameters were not altered by diminishing hepatic function; therefore, no dose adjustment for lamivudine is required for patients with impaired hepatic function. Safety and efficacy of lamivudine have not been established in the presence of decompensated liver disease.

Pediatric Patients: The pharmacokinetics of lamivudine have been studied after either single or repeat doses of EPIVIR in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral solution according to the recommended dosage regimen achieved approximately 25% lower plasma concentrations of lamivudine compared with HIV-1-infected adults. Pediatric subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults. The absolute bioavailability of both EPIVIR tablets and oral solution are lower in children than adults. The relative bioavailability of EPIVIR oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects

despite no difference in adults. The mechanisms for the diminished absolute bioavailability of lamivudine and relative bioavailability of lamivudine solution are unknown.

The pharmacokinetics of lamivudine dosed once daily in HIV-1-infected pediatric subjects aged 3 months through 12 years was evaluated in 3 trials (PENTA-15 [n = 17], PENTA 13 [n = 19], and ARROW PK [n = 35]). All 3 trials were 2-period, crossover, open-label pharmacokinetic trials of twice- versus once-daily dosing of abacavir and lamivudine. These 3 trials demonstrated that once-daily dosing provides similar AUC_{0-24} to twice-daily dosing of lamivudine at the same total daily dose when comparing the dosing regimens within the same formulation (i.e., either the oral solution or the tablet formulation). The mean C_{max} was approximately 80% to 90% higher with lamivudine once-daily dosing compared with twice-daily dosing.

Table 8. Pharmacokinetic Parameters (Geometric Mean [95% CI]) after Repeat Dosing of Lamivudine in 3 Pediatric Trials

	Trial (Number of Subjects)					
	ARROW PK (n = 35)		PENTA-13 (n = 19)		PENTA-15 (n = 17)[a]	
Age Range	3-12 years		2-12 years		3-36 months	
Formulation	Tablet		Solution and Tablet[b]		Solution	
Parameter	Once Daily	Twice Daily	Once Daily	Twice Daily	Once Daily	Twice Daily
C_{max} (mcg/mL)	3.17 (2.76, 3.64)	1.80 (1.59, 2.04)	2.09 (1.80, 2.42)	1.11 (0.96, 1.29)	1.87 (1.65, 2.13)	1.05 (0.88, 1.26)
$AUC_{(0-24)}$ (mcg•h/mL)	13.0 (11.4, 14.9)	12.0 (10.7, 13.4)	9.80 (8.64, 11.1)	8.88 (7.67, 10.3)	8.66 (7.46, 10.1)	9.48 (7.89, 11.4)

[a] N = 16 for PENTA-15 C_{max}.

[b] Five subjects in PENTA-13 received lamivudine tablets.

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

Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants aged up to 1 week in 2 trials in South Africa. In these trials, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric subjects (aged over 3 months) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the

age-ranges over 3 months old *[see Adverse Reactions (6.2)]*.

Geriatric Patients: The pharmacokinetics of lamivudine after administration of EPIVIR to subjects over 65 years have not been studied *[see Use in Specific Populations (8.5)]*.

Gender: There are no significant gender differences in lamivudine pharmacokinetics.

Race: There are no significant racial differences in lamivudine pharmacokinetics.

Drug Interactions

Interferon Alfa: There was no significant pharmacokinetic interaction between lamivudine and interferon alfa in a trial of 19 healthy male subjects *[see Warnings and Precautions (5.4)]*.

Ribavirin: In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV-1/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n = 18), stavudine (n = 10), or zidovudine (n = 6) were coadministered as part of a multi-drug regimen to HIV-1/HCV co-infected subjects *[see Warnings and Precautions (5.4)]*.

Trimethoprim/Sulfamethoxazole: Lamivudine and TMP/SMX were coadministered to 14 HIV-1-positive subjects in a single-center, open-label, randomized, crossover trial. Each subject received treatment with a single 300-mg dose of lamivudine and TMP 160 mg/SMX 800 mg once a day for 5 days with concomitant administration of lamivudine 300 mg with the fifth dose in a crossover design. Coadministration of TMP/SMX with lamivudine resulted in an increase of 43% ± 23% (mean ± SD) in lamivudine AUC∞, a decrease of 29% ± 13% in lamivudine oral clearance, and a decrease of 30% ± 36% in lamivudine renal clearance. The pharmacokinetic properties of TMP and SMX were not altered by coadministration with lamivudine *[see Drug Interactions (7.3)]*.

Zidovudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-1-infected adult subjects given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 h) *[see Drug Interactions (7.4)]*.

12.4 Microbiology

Mechanism of Action

Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α, β, and γ.

Antiviral Activity

The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC_{50} values (50% effective concentrations) were in the range of 0.003 to 15 µM (1 µM = 0.23 mcg per mL). HIV-1 from therapy-naive subjects with no amino acid substitutions associated with resistance gave median EC_{50} values of 0.429 µM (range: 0.200 to 2.007 µM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 µM (range: 1.37 to 3.68 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC_{50} values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. Please see the full prescribing information for EPIVIR-HBV for information regarding the inhibitory activity of lamivudine against HBV.

Resistance

Lamivudine-resistant variants of HIV-1 have been selected in cell culture. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from subjects. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In subjects receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most subjects became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some subjects harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Lamivudine-resistant HBV isolates develop substitutions (rtM204V/I) in the YMDD motif of the catalytic domain of the viral reverse transcriptase. rtM204V/I substitutions are frequently accompanied by other substitutions (rtV173L, rtL180M) which enhance the level of lamivudine resistance or act as compensatory mutations improving replication efficiency. Other substitutions detected in lamivudine-resistant HBV isolates include: rtL80I and rtA181T. Similar HBV mutants have been reported in HIV-1-infected subjects who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus *[see Warnings and Precautions (5.2)]*.

Cross-resistance

Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some subjects treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-therapy HIV-1 Isolates from Subjects with Virologic Failure

Trial EPV20001: Fifty-three of 554 (10%) subjects enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level greater than or equal to 400 copies per mL) by Week 48. Twenty-eight subjects were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of subjects in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 $\log_{10}$ copies per mL and 4.6 $\log_{10}$ copies per mL, respectively.

Genotypic analysis of on-therapy isolates from 22 subjects identified as virologic failures in the lamivudine once-daily group showed that isolates from 0 of 22 subjects contained treatment-emergent amino acid substitutions associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10 of 22 subjects contained treatment-emergent amino acid substitutions associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8 of 22 subjects contained a treatment-emergent lamivudine resistance-associated substitution (M184I or M184V).

Genotypic analysis of on-therapy isolates from subjects (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 1 of 22 subjects contained treatment-emergent zidovudine resistance substitutions, isolates from 7 of 22 contained treatment-emergent efavirenz resistance substitutions, and isolates from 5 of 22 contained treatment-emergent lamivudine resistance substitutions.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13) receiving lamivudine once daily showed that isolates from 12 of 13 subjects were susceptible to zidovudine; isolates from 8 of 13 subjects exhibited a 25- to 295-fold decrease in susceptibility to efavirenz, and isolates from 7 of 13 subjects showed an 85- to 299-fold decrease in susceptibility to lamivudine.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from subjects (n = 13) receiving lamivudine twice daily showed that isolates from all 13 subjects were susceptible to zidovudine; isolates from 3 of 13 subjects exhibited a 21- to 342-fold decrease in susceptibility to efavirenz, and isolates from 4 of 13 subjects exhibited a 29- to 159-fold decrease in susceptibility to lamivudine.

Trial EPV40001: Fifty subjects received zidovudine 300 mg twice daily plus abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 subjects received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice-daily. The median baseline plasma HIV-1 RNA levels for subjects in the 2 groups were 4.79 $\log_{10}$ copies per mL and 4.83 $\log_{10}$ copies per mL, respectively. Fourteen of 50 subjects in the lamivudine once-daily treatment group and 9 of 50 subjects in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from subjects (n = 9) in the lamivudine

once-daily treatment group showed that isolates from 6 subjects had an abacavir and/or lamivudine resistance-associated substitution M184V alone. On-therapy isolates from subjects (n = 6) receiving lamivudine twice daily showed that isolates from 2 subjects had M184V alone, and isolates from 2 subjects harbored the M184V substitution in combination with zidovudine resistance-associated amino acid substitutions.

Phenotypic analysis of on-therapy isolates from subjects (n = 6) receiving lamivudine once daily showed that HIV-1 isolates from 4 subjects exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 subjects were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from subjects (n = 4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 subject exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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-1 infection.

Mutagenesis

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 per kg, producing plasma levels of 35 to 45 times those in humans at the recommended dose for HIV-1 infection.

Impairment of Fertility

In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg per 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.

14 CLINICAL STUDIES

The use of EPIVIR is based on the results of clinical trials in HIV-1-infected subjects in combination regimens with other antiretroviral agents. Information from trials with clinical endpoints or a combination of CD4+ cell counts and HIV-1 RNA measurements is included below as documentation of the contribution of lamivudine to a combination regimen in controlled trials.

14.1 Adult Subjects

Clinical Endpoint Trial

NUCB3007 (CAESAR) was a multi-center, double-blind, placebo-controlled trial comparing continued current therapy (zidovudine alone [62% of subjects] or zidovudine with didanosine or zalcitabine [38% of subjects]) to the addition of EPIVIR or EPIVIR plus an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), randomized 1:2:1. A total of 1,816 HIV-1-infected adults with 25 to 250 CD4+ cells per mm^3 (median = 122 cells per mm^3) at baseline were enrolled: median age was 36 years, 87% were male, 84% were nucleoside-experienced, and 16% were therapy-naive. The median duration on trial was 12 months. Results are summarized in Table 9.

Table 9. Number of Subjects (%) with at Least One HIV-1 Disease Progression Event or Death

Endpoint	Current Therapy (n = 460)	EPIVIR plus Current Therapy (n = 896)	EPIVIR plus an NNRTI[a] plus Current Therapy (n = 460)
HIV-1 progression or death	90 (19.6%)	86 (9.6%)	41 (8.9%)
Death	27 (5.9%)	23 (2.6%)	14 (3.0%)

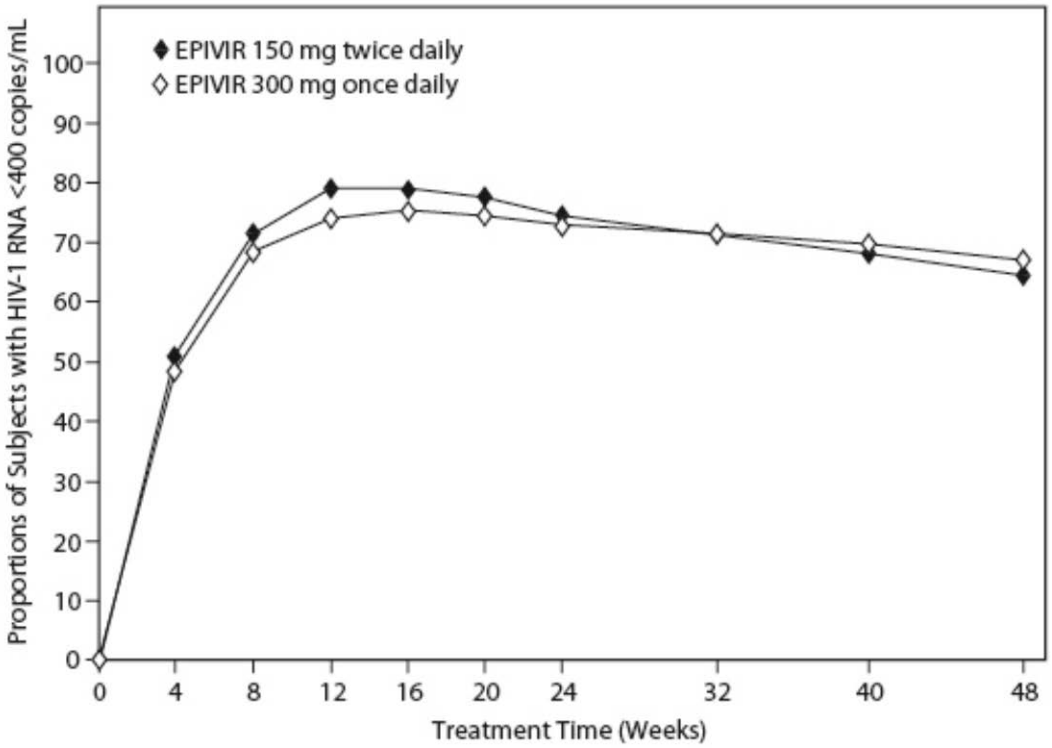
[a] An investigational non-nucleoside reverse transcriptase inhibitor not approved in the United States.

Surrogate Endpoint Trials

Dual Nucleoside Analogue Trials: Principal clinical trials in the initial development of lamivudine compared lamivudine/zidovudine combinations with zidovudine monotherapy or with zidovudine plus zalcitabine. These trials demonstrated the antiviral effect of lamivudine in a 2-drug combination. More recent uses of lamivudine in treatment of HIV-1 infection incorporate it into multiple-drug regimens containing at least 3 antiretroviral drugs for enhanced viral suppression.

Dose Regimen Comparison Surrogate Endpoint Trials in Therapy-naive Adults: EPV20001 was a multi-center, double-blind, controlled trial in which subjects were randomized 1:1 to receive EPIVIR 300 mg once daily or EPIVIR 150 mg twice daily, in combination with zidovudine 300 mg twice daily and efavirenz 600 mg once daily. A total of 554 antiretroviral treatment-naive HIV-1-infected adults enrolled: male (79%), white (50%), median age of 35 years, baseline CD4+ cell counts of 69 to 1,089 cells per mm^3 (median = 362 cells per mm^3), and median baseline plasma HIV-1 RNA of 4.66 $\log_{10}$ copies per mL. Outcomes of treatment through 48 weeks are summarized in Figure 1 and Table 10.

Figure 1. Virologic Response through Week 48, EPV20001[ab] (Intent-to-Treat)



[a] Roche AMPLICOR HIV-1 MONITOR.

[b] Responders at each visit are subjects who had achieved and maintained HIV-1 RNA less than 400 copies per mL without discontinuation by that visit.

Table 10. 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[a]	67%	65%
Virologic failure[b]	8%	8%
Discontinued due to clinical progression	<1%	0%
Discontinued due to adverse events	6%	12%
Discontinued due to other reasons[c]	18%	14%

[a] Achieved confirmed plasma HIV-1 RNA less than 400 copies per mL and maintained through 48 weeks.

[b] 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.

[c] Includes consent withdrawn, lost to follow-up, protocol violation, data outside the trial-defined

schedule, and randomized but never initiated treatment.

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

A small, randomized, open-label pilot trial, EPV40001, was conducted in Thailand. A total of 159 treatment-naive adult subjects (male 32%, Asian 100%, median age 30 years, baseline median CD4+ cell count 380 cells per mm^3, median plasma HIV-1 RNA 4.8 $\log_{10}$ copies per mL) were enrolled. Two of the treatment arms in this trial 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 subjects with HIV-1 RNA below 400 copies per mL were 61% (33 of 54) in the group randomized to once-daily lamivudine and 75% (39 of 52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies per mL were 54% (29 of 54) in the once-daily lamivudine group and 67% (35 of 52) in the all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells per mm^3 in the once-daily lamivudine group and 216 cells per mm^3 in the all-twice-daily group.

14.2 Pediatric Subjects

Clinical Endpoint Trial

ACTG300 was a multi-center, randomized, double-blind trial that provided for comparison of EPIVIR plus RETROVIR (zidovudine) with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive (less than or equal to 56 days of antiretroviral therapy) pediatric subjects 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-white. The mean baseline CD4+ cell count was 868 cells per mm^3 (mean: 1,060 cells per mm^3 and range: 0 to 4,650 cells per mm^3 for subjects aged less than or equal to 5 years; mean: 419 cells per mm^3 and range: 0 to 1,555 cells per mm^3 for subjects aged over 5 years) and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies per mL. The median duration on trial was 10.1 months for the subjects receiving EPIVIR plus RETROVIR and 9.2 months for subjects receiving didanosine monotherapy. Results are summarized in Table 11.

Table 11. Number of Subjects (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)

Endpoint	EPIVIR plus RETROVIR (n = 236)	Didanosine (n = 235)
HIV-1 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%)

Once-daily Dosing

ARROW (COL105677) was a 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric subjects. HIV–1-infected, treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first-line regimen containing EPIVIR and abacavir, dosed twice daily according to World Health Organization recommendations. After a minimum of 36 weeks on treatment, subjects were given the option to participate in Randomization 3 of the ARROW trial, comparing the safety and efficacy of once-daily dosing with twice-daily dosing of EPIVIR and abacavir, in combination with a third antiretroviral drug, for an additional 96 weeks. Of the 1,206 original ARROW subjects, 669 participated in Randomization 3. Virologic suppression was not a requirement for participation: at baseline for Randomization 3 (following a minimum of 36 weeks of twice-daily treatment), 75% of subjects in the twice-daily cohort were virologically suppressed, compared with 71% of subjects in the once-daily cohort.

The proportion of subjects with HIV-1 RNA of less than 80 copies per mL through 96 weeks is shown in Table 12. The differences between virologic responses in the two treatment arms were comparable across baseline characteristics for gender and age.

Table 12. Virologic Outcome of Randomized Treatment at Week 96[a] (ARROW Randomization 3)

Outcome	EPIVIR plus Abacavir Twice-daily Dosing (n = 333)	EPIVIR plus Abacavir Once-daily Dosing (n = 336)
HIV-1 RNA <80 copies/mL[b]	70%	67%
HIV-1 RNA ≥80 copies/mL[c]	28%	31%
No virologic data		
Discontinued due to adverse event or death	1%	<1%
Discontinued study for other reasons[d]	0%	<1%
Missing data during window but on study	1%	1%

[a] Analyses were based on the last observed viral load data within the Week 96 window.

[b] Predicted difference (95% CI) of response rate is -4.5% (-11% to 2%) at Week 96.

[c] Includes subjects who discontinued due to lack or loss of efficacy or for reasons other than an adverse event or death, and had a viral load value of greater than or equal to 80 copies per mL, or subjects who had a switch in background regimen that was not permitted by the protocol.

[d] Other includes reasons such as withdrew consent, loss to follow-up, etc. and the last available HIV-1 RNA less than 80 copies per mL (or missing).

16 HOW SUPPLIED/STORAGE AND HANDLING

EPIVIR Scored Tablets, 150 mg

White, diamond-shaped, scored, film-coated tablets debossed with “GX CJ7” on both sides.

Bottle of 60 tablets (NDC 49702-203-18) with child-resistant closure.

EPIVIR Tablets, 300 mg

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 49702-204-13) with child-resistant closure.

Recommended Storage:

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

EPIVIR Oral Solution, 10 mg per mL

A clear, colorless to pale yellow, strawberry-banana-flavored liquid, contains 10 mg of lamivudine in each 1 mL.

Plastic bottle of 240 mL (NDC 49702-205-48) with child-resistant closure. This product does not require reconstitution.

Recommended Storage:

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Lactic Acidosis/Hepatomegaly

Inform patients that some HIV medicines, including EPIVIR, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Warnings and Precautions (5.1)]*.

HIV-1/HBV Co-infection

Inform patients co-infected with HIV-1 and HBV that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Advise patients to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.

Differences in Formulations of EPIVIR

Advise patients 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-1 treatment regimen of a patient co-infected with HIV-1 and HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used *[see Warnings and Precautions (5.2)]*.

Use with Other Lamivudine- and Emtricitabine-containing Products

EPIVIR should not be coadministered with drugs containing lamivudine or emtricitabine, including COMBIVIR (lamivudine/zidovudine) tablets, EPZICOM (abacavir sulfate and lamivudine) tablets, TRIUMEQ (dolutegravir, abacavir, lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine), STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate), TRUVADA (emtricitabine and tenofovir), or COMPLERA (rilpivirine/emtricitabine/tenofovir) *[see Warnings and Precautions (5.3)]*.

HIV-1/HCV Co-infection:

Inform patients with HIV-1/HCV co-infection that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.4)]*.

Risk of Pancreatitis

Advise parents or guardians to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.5)]*.

Redistribution/Accumulation of Body Fat

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including EPIVIR, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.7)]*.

Sucrose Content of EPIVIR Oral Solution

Advise diabetic patients that each 15-mL dose of EPIVIR oral solution contains 3 grams of sucrose (1 mL = 200 mg of sucrose) *[see Description (11)]*.

Information about HIV-1 Infection

EPIVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients must remain on continuous HIV therapy to control HIV-1 infection and decrease HIV-related illness. Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician when using EPIVIR.

Patients should be informed to take all HIV medications exactly as prescribed. If you miss a dose of EPIVIR, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare provider.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not re-use or share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- Continue to practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- Female patients should be advised not to breastfeed. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Manufactured for:

ViiV Healthcare
Research Triangle Park, NC 27709

by:

GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured under agreement from
Shire Pharmaceuticals Group plc
Basingstoke, UK

EPV:XPI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION

EPIVIR® (EP-i-veer)
(lamivudine)
tablets

EPIVIR (EP-i-veer)
(lamivudine)
oral solution

What is the most important information I should know about EPIVIR?

EPIVIR can cause serious side effects, including:

- **Build-up of an acid in your blood (lactic acidosis).** Lactic acidosis can happen in some people who take EPIVIR or similar medicines (nucleoside analogs). Lactic acidosis is a serious medical emergency that can lead to death. Lactic acidosis can be hard to identify early because the symptoms could seem like symptoms of other health problems. **Call your healthcare provider right away if you get any of the following symptoms that could be signs of lactic acidosis:**
  - feel very weak or tired
  - unusual (not normal) muscle pain
  - trouble breathing
  - stomach pain with nausea and vomiting
  - feel cold, especially in your arms and legs
  - feel dizzy or light-headed
  - have a fast or irregular heartbeat
- **Severe liver problems.** Severe liver problems can happen in people who take EPIVIR or similar medicines. In some cases these liver problems can lead to death. Your liver may become large (hepatomegaly) and you may develop fat in your liver (steatosis) when you take EPIVIR. **Call your healthcare provider right away if you get any of the following signs of liver problems:**
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or “tea-colored” urine
  - light-colored stools (bowel movements)
  - loss of appetite for several days or longer
  - nausea
  - pain, aching, or tenderness on the right side of your stomach area

You may be more likely to get lactic acidosis or severe liver problems if you are female, very overweight (obese), or have been taking nucleoside analog medicines for a long time or have risks for liver problems.

- **Worsening of hepatitis B infection.** If you have HIV-1 (Human Immunodeficiency Virus) and hepatitis B virus (HBV) infection, your HBV may get worse (flare-up) if you stop taking EPIVIR. A “flare-up” is when your HBV infection suddenly returns in a worse way than before. Worsening liver disease from HBV can be serious and may lead to death.
  - Do not run out of EPIVIR. Refill your prescription or talk to your healthcare provider

before your EPIVIR is all gone.

- Do not stop EPIVIR without first talking to your healthcare provider.
- If you stop taking EPIVIR, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver.

What is EPIVIR?

EPIVIR is a prescription HIV-1 medicine used with other antiretroviral medicines to treat HIV-1 infections in adults and children aged 3 months and older. HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

EPIVIR tablets and oral solution (used to treat HIV-1 infection) contain a higher dose of the same active ingredient (lamivudine) than is in the medicine EPIVIR-HBV tablets and oral solution (used to treat HBV). If you have both HIV-1 and HBV, you should not use EPIVIR-HBV to treat your infections.

It is not known if EPIVIR is safe and effective in children under 3 months of age.

When used with other antiretroviral medicines to treat HIV-1 infection, EPIVIR may help:

- reduce the amount of HIV-1 in your blood. This is called “viral load”.
- increase the number of CD4+ (T) cells in your blood, which help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may help improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

EPIVIR does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others:

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.

Ask your healthcare provider if you have any questions about how to prevent passing HIV to other people.

Who should not take EPIVIR?

Do not take EPIVIR if you are allergic to lamivudine or any of the ingredients in EPIVIR. **See “What are the ingredients in EPIVIR?”.**

Do not take EPIVIR if you also take:

- other medicines that contain lamivudine (COMBIVIR®, EPIVIR-HBV®, EPZICOM®,

TRIZIVIR®, TRIUMEQ®)
- medicines that contain emtricitabine (ATRIPLA®, COMPLERA®, EMTRIVA®, STRIBILD®, TRUVADA®)

What should I tell my healthcare provider before taking EPIVIR?

Before you take EPIVIR, tell your healthcare provider if you:

- have or had liver problems, including hepatitis B or C infection.
- have kidney problems.
- have diabetes. Each 15-mL dose (150 mg) of EPIVIR oral solution contains 3 grams of sucrose.
- have any other medical condition.
- are pregnant or plan to become pregnant. Taking EPIVIR during pregnancy has not been associated with an increased risk of birth defects. Tell your healthcare provider if you become pregnant while taking EPIVIR.

  Pregnancy Registry. There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take EPIVIR.**
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. **Keep a list of your medicines to show your healthcare provider and pharmacist. Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take EPIVIR with other medicines.

How should I take EPIVIR?

- Take EPIVIR exactly as your healthcare provider tells you.
- Do not change your dose or stop taking EPIVIR without talking with your healthcare provider.
- For children 3 months and older, your healthcare provider will prescribe a dose of EPIVIR based on your child's body weight.
- Take EPIVIR by mouth, with or without food.
- Tell your healthcare provider if you have trouble swallowing tablets. EPIVIR also comes as a liquid (oral solution).
- Do not skip doses. If you miss a dose of EPIVIR, take it as soon as you remember. Do not take 2 doses at the same time. If you are not sure about your dosing, call your healthcare

provider.

- If you take too much EPIVIR, call your healthcare provider or go to the nearest hospital emergency room right away. It is important to stay under your healthcare provider's care while taking EPIVIR.

What are the possible side effects of EPIVIR?

EPIVIR can cause serious side effects. See "What is the most important information I should know about EPIVIR?".

- **Use with interferon and ribavirin-based treatment.** Worsening of liver disease that has sometimes led to death has happened in people infected with both HIV-1 and hepatitis C virus who are taking antiretroviral medicines, and are also being treated for hepatitis C with interferon with or without ribavirin. If you are taking EPIVIR and interferon with or without ribavirin, tell your healthcare provider if you have any new symptoms.
- **Risk of inflammation of the pancreas (pancreatitis).** Children may be at risk for developing pancreatitis during treatment with EPIVIR if they:
  - have taken nucleoside analogue medicines in the past
  - have a history of pancreatitis
  - have other risk factors for pancreatitis

Call your healthcare provider right away if your child develops signs and symptoms of pancreatitis including severe upper stomach-area pain, with or without nausea and vomiting. Your healthcare provider may tell you to stop giving EPIVIR to your child if their symptoms and blood test results show that your child may have pancreatitis.

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.
- **Changes in body fat can happen in people who take HIV-1 medicines.** These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these problems are not known.

The most common side effects of EPIVIR in adults include:

- headache
- nausea
- generally not feeling well
- tiredness
- nasal signs and symptoms
- diarrhea
- cough

The most common side effects of EPIVIR in children include fever and cough.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of EPIVIR. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EPIVIR?

- Store EPIVIR tablets and oral solution at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep bottles of EPIVIR oral solution tightly closed.

Keep EPIVIR and all medicines out of the reach of children.

General information about the safe and effective use of EPIVIR.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EPIVIR for a condition for which it was not prescribed. Do not give EPIVIR to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about EPIVIR that is written for health professionals.

For more information, go to www.viivhealthcare.com or call 1-877-844-8872.

What are the ingredients in EPIVIR?

Active ingredient: lamivudine

Inactive ingredients:

EPIVIR scored 150-mg film-coated tablets: hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

EPIVIR 300-mg film-coated tablets: black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

EPIVIR oral solution: artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg per mL).

This Patient Information has been approved by the U.S. Food and Drug Administration.

not endorse the ViiV Healthcare group of companies or its products.

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Research Triangle Park, NC 27709

by:

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