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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EMTRICITABINE capsules, for oral use

Initial U.S. Approval: 2003

### WARNING: POSTTREATMENT EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

Emtricitabine is not approved for the treatment of chronic Hepatitis B virus (HBV) infection. Severe acute exacerbations of Hepatitis B have been reported in patients who have discontinued emtricitabine. Hepatic function should be monitored closely in patients coinfecting with HIV-1 and HBV. If appropriate, initiation of anti-Hepatitis B therapy may be warranted. (5.1)

### INDICATIONS AND USAGE

Emtricitabine, a nucleoside analog HIV-1 reverse transcriptase inhibitor, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

### DOSAGE AND ADMINISTRATION

- Emtricitabine capsule may be taken without regard to food. (2.1)
- Adult Patients (18 years of age and older) (2.2):
  - Emtricitabine capsules: one 200 mg capsule administered once daily orally.
- Pediatric Patients (3 months through 17 years) (2.4):
  - Emtricitabine capsules: for children weighing more than 33 kg who can swallow an intact capsule, one 200 mg capsule administered once daily orally.
- Dose interval adjustment in adult patients with renal impairment (2.5):

Formulation	Creatinine Clearance (mL/min)			
	≥50 mL/min	30 to 49 mL/min	15 to 29 mL/min	<15 mL/min or on hemodialysis <sup>a</sup>
Capsule (200 mg)	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours

- a. Hemodialysis Patients: If dosing on day of dialysis, give dose after dialysis.

### DOSAGE FORMS AND STRENGTHS

- Capsules: 200 mg (3)

### CONTRAINDICATIONS

Emtricitabine capsules are contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products. (4)

### WARNINGS AND PRECAUTIONS

- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.2)
- Products with same active ingredient: Do not use with other emtricitabine-containing products (e.g., ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, and TRUVADA). (5.3)
- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (5.4)

### ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10%) are headache, diarrhea, nausea, fatigue, dizziness, depression, insomnia, abnormal dreams, rash, abdominal pain, asthenia, increased cough, and rhinitis. Skin hyperpigmentation was very common (≥10%) in pediatric patients. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Micro Labs USA, Inc. at 1-855-875-7814 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Nursing mothers: Women infected with HIV should be instructed not to breastfeed. (8.3)
- Pediatrics: Dose adjustment based on age and weight. (2.3, 2.4, 12.3)

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

Revised: 08/2018

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## FULL PRESCRIBING INFORMATION

### **WARNING: POSTTREATMENT EXACERBATION OF HEPATITIS B**

**Emtricitabine is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of emtricitabine have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued emtricitabine. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue emtricitabine. If appropriate, initiation of anti-hepatitis B therapy may be warranted [See Warnings and Precautions (5.1)].**

## **1 INDICATIONS AND USAGE**

Emtricitabine capsules are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Additional important information regarding the use of emtricitabine capsules for the treatment of HIV-1 Infection:

Emtricitabine capsules should not be coadministered with ATRIPLA<sup>®</sup>, COMPLERA<sup>®</sup>, DESCOVY<sup>®</sup>, GENVOYA<sup>®</sup>, ODEFSEY<sup>®</sup>, STRIBILD<sup>®</sup>, TRUVADA<sup>®</sup>, or lamivudine-containing products [See Warnings and Precautions (5.3)].

In treatment-experienced patients, the use of emtricitabine capsules should be guided by laboratory testing and treatment history [See Clinical Pharmacology (12.4)].

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Recommended Dose**

Emtricitabine capsules may be taken without regard to food.

### **2.2 Adult Patients (18 years of age and older)**

**Emtricitabine capsules:** One 200 mg capsule administered once daily orally.

### **2.4 Pediatric Patients (3 months through 17 years)**

**Emtricitabine capsules:** For children weighing more than 33 kg who can swallow an intact capsule, one 200 mg capsule administered once daily orally.

### **2.5 Dose Adjustment in Adult Patients with Renal Impairment**

Significantly increased drug exposures were seen when emtricitabine capsules were administered to subjects with renal impairment [See *Clinical Pharmacology (12.3)*]. Therefore, the dosing interval or dose of emtricitabine capsules should be adjusted in patients with baseline creatinine clearance less than 50 mL per min using the following guidelines (Table 1). The safety and effectiveness of these dose adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

**Table 1 Dose Adjustment in Adult Patients with Renal Impairment**

Formulation	Creatinine Clearance (mL/min)			
	≥50 mL/min	30 to 49 mL/min	15 to 29 mL/min	<15 mL/min or on hemodialysis <sup>a</sup>
Capsule (200 mg)	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours

a. Hemodialysis Patients: If dosing on day of dialysis, give dose after dialysis

Although there are insufficient data to recommend a specific dose adjustment of emtricitabine capsules in pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval similar to adjustments for adults should be considered.

### 3 DOSAGE FORMS AND STRENGTHS

Emtricitabine is available as capsules.

Emtricitabine capsules, containing 200 mg of emtricitabine, are Size '1' Hard gelatin Capsule with a light blue opaque cap and white opaque body, printed with 'M' in black on the cap and '18' in black on the body, filled with off white granular powder.

### 4 CONTRAINDICATIONS

Emtricitabine capsules are contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Patients Coinfected with HIV-1 and HBV

It is recommended that all patients with HIV-1 be tested for the presence of chronic Hepatitis B virus (HBV) before initiating antiretroviral therapy. Emtricitabine is not approved for the treatment of chronic HBV infection, and the safety and efficacy of emtricitabine have not been established in patients coinfecting with HBV and HIV-1. Severe acute exacerbations of Hepatitis B have been reported in patients after the discontinuation of emtricitabine. In some patients infected with HBV and treated with emtricitabine, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Hepatic function should be monitored

closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV-1 and HBV and discontinue emtricitabine. If appropriate, initiation of anti-Hepatitis B therapy may be warranted.

## **5.2 Lactic Acidosis/Severe Hepatomegaly with Steatosis**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, alone or in combination with other antiretrovirals. Treatment with emtricitabine 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).

## **5.3 Coadministration with Related Products**

Emtricitabine is a component of ATRIPLA (a fixed-dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate [tenofovir DF]), COMPLERA (a fixed-dose combination of emtricitabine, rilpivirine, and tenofovir DF), DESCOVY (a fixed-dose combination of emtricitabine and tenofovir alafenamide), ODEFSEY (a fixed-dose combination of emtricitabine, rilpivirine, and tenofovir alafenamide), GENVOYA (a fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide), STRIBILD (a fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir DF), and TRUVADA (a fixed-dose combination of emtricitabine and tenofovir DF). Emtricitabine should not be coadministered with ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, or TRUVADA. Due to similarities between emtricitabine and lamivudine, emtricitabine should not be coadministered with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Triumeq (abacavir sulfate/dolutegravir/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine).

## **5.4 New Onset or Worsening Renal Impairment**

Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of emtricitabine is recommended for patients with impaired renal function [*See Dosage and Administration (2.5) and Clinical Pharmacology (12.3)*].

## **5.5 Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine. 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.

## **6 ADVERSE REACTIONS**

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

- Severe acute exacerbations of Hepatitis B [*See Boxed Warning, Warnings and Precautions (5.1)*].
- Lactic acidosis/severe hepatomegaly with steatosis [*See Warnings and Precautions (5.2)*]
- Immune Reconstitution Syndrome [*See Warnings and Precautions (5.5)*].

### **6.1 Adverse Reactions from Clinical Trials Experience**

#### **Clinical Trials in Adult Subjects**

More than 2,000 adult subjects with HIV-1 infection have been treated with emtricitabine alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in clinical trials.

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

The most common adverse reactions (incidence greater than or equal to 10%, any severity) identified from any of the three large, controlled clinical trials include headache, diarrhea, nausea, fatigue, dizziness, depression, insomnia, abnormal dreams, rash, abdominal pain, asthenia, increased cough, and rhinitis.

*Studies 301A and 303 - Treatment Emergent Adverse Reactions:* The most common adverse reactions that occurred in subjects receiving emtricitabine with other antiretroviral agents in clinical trials 301A and 303 were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of subjects discontinued participation in the clinical trials due to these events. All adverse reactions were reported with similar frequency in emtricitabine and control treatment groups with the exception of skin discoloration, which was reported with higher frequency in the emtricitabine treated group.

Skin discoloration, manifested by hyperpigmentation on the palms and/or soles, was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

A summary of emtricitabine treatment-emergent clinical adverse reactions in Studies 301A and 303 is provided in Table 2.

**Table 2 Selected Treatment-Emergent Adverse Reactions (All Grades, Regardless of Causality) Reported in  $\geq 3\%$  of Emtricitabine-Treated Subjects in Either Study 301A or 303 (0 to 48 Weeks)**

	303		301A	
	Emtricitabine + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	Emtricitabine + Didanosine + Efavirenz (N=286)	Stavudine + Didanosine + Efavirenz (N=285)
Body as a Whole				
Abdominal pain	8%	11%	14%	17%
Asthenia	16%	10%	12%	17%
Headache	13%	6%	22%	25%
Digestive System				
Diarrhea	23%	18%	23%	32%
Dyspepsia	4%	5%	8%	12%
Nausea	18%	12%	13%	23%
Vomiting	9%	7%	9%	12%
Musculoskeletal				
Arthralgia	3%	4%	5%	6%
Myalgia	4%	4%	6%	3%
Nervous System				
Abnormal dreams	2%	<1%	11%	19%
Depressive disorders	6%	10%	9%	13%
Dizziness	4%	5%	25%	26%
Insomnia	7%	3%	16%	21%
Neuropathy/peripheral neuritis	4%	3%	4%	13%
Paresthesia	5%	7%	6%	12%
Respiratory				
Increased cough	14%	11%	14%	8%
Rhinitis	18%	12%	12%	10%
Skin				
Rash event <sup>a</sup>	17%	14%	30%	33%

a. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, and allergic reaction.

*Studies 301A and 303 - Laboratory Abnormalities:* Laboratory abnormalities in these trials occurred with similar frequency in the emtricitabine and comparator groups. A summary of Grades 3 to 4 laboratory abnormalities is provided in Table 3.

**Table 3 Treatment-Emergent Grades 3 to 4 Laboratory Abnormalities Reported in  $\geq 1\%$  of Emtricitabine-Treated Subjects in Either Study 301A or 303**

	303	301A
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	<b>Emtricitabine + ZDV/d4T + NNRTI/PI (N=294)</b>	<b>Lamivudine + ZDV/d4T + NNRTI/PI (N=146)</b>	<b>Emtricitabine + Didanosine + Efavirenz (N=286)</b>	<b>Stavudine + Didanosine + Efavirenz (N=285)</b>
Percentage with grade 3 or grade 4 laboratory abnormality	31%	28%	34%	38%
ALT (>5 x ULN <sup>a</sup> )	2%	1%	5%	6%
AST (>5 x ULN)	3%	<1%	6%	9%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine kinase (>4 x ULN)	11%	14%	12%	11%
Neutrophils (<750 mm <sup>3</sup> )	5%	3%	5%	7%
Pancreatic amylase (>2 x ULN)	2%	2%	<1%	1%
Serum amylase (>2 x ULN)	2%	2%	5%	10%
Serum glucose <40 or >250 mg/dL)	3%	3%	2%	3%
Serum lipase (>2 x ULN)	<1%	<1%	1%	2%
Triglycerides (>750 mg/dL)	10%	8%	9%	6%

a. ULN = Upper limit of normal

*Study 934 - Treatment Emergent Adverse Reactions:* In Study 934, 511 antiretroviral-naïve subjects received either VIREAD<sup>®</sup> + emtricitabine administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse reactions observed in this trial were generally consistent with those seen in previous trials in treatment-experienced or treatment-naïve subjects (Table 4).

**Table 4 Selected Treatment-Emergent Adverse Reactions<sup>a</sup> (Grades 2 to 4) Reported in ≥5% in Any Treatment Group in Study 934 (0 to 144 Weeks)**

	<b>TDF<sup>b</sup> + Emtricitabine + EFV N=257</b>	<b>AZT/3TC + EFV N=254</b>
Gastrointestinal Disorder		
Diarrhea	9%	5%
Nausea	9%	7%
Vomiting	2%	5%
General Disorders and Administration Site Condition		
Fatigue	9%	8%
Infections and Infestations		
Sinusitis	8%	4%
Upper respiratory tract infections	8%	5%
Nasopharyngitis	5%	3%

Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	9%	7%
Insomnia	5%	7%
Skin and Subcutaneous Tissue Disorders		
Rash event <sup>c</sup>	7%	9%

- a. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
- b. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + Emtricitabine with efavirenz.
- c. Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculopapular, rash pruritic, and rash vesicular.

*Study 934 – Laboratory Abnormalities:* Significant laboratory abnormalities observed in this trial are shown in Table 5.

**Table 5 Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0 to 144 Weeks)**

	TDF <sup>a</sup> + Emtricitabine + EFV	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Fasting Cholesterol (>240 mg/dL)	22%	24%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hemoglobin (<8 mg/dL)	0%	4%
Hyperglycemia (>250 mg/dL)	2%	1%
Hematuria (>75 RBC/HPF)	3%	2%
Glycosuria (3+)	<1%	1%
Neutrophils (<750/mm <sup>3</sup> )	3%	5%

Fasting Triglycerides (>750 mg/dL)	4%	2%
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- a. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + Emtricitabine with efavirenz.

### Clinical Trials in Pediatric Subjects

Assessment of adverse reactions is based on data from Study 203, an open label, uncontrolled trial of 116 HIV-1 infected pediatric subjects who received emtricitabine through 48 weeks. The adverse reaction profile in pediatric subjects was generally comparable to that observed in clinical trials of emtricitabine in adult subjects [See Adverse Reactions (6.1)]. Hyperpigmentation was more frequent in children. Additional adverse reactions identified from this trial include anemia.

Selected treatment-emergent adverse events, regardless of causality, reported in subjects during 48 weeks of treatment were the following: infection (44%), hyperpigmentation (32%), increased cough (28%), vomiting (23%), otitis media (23%), rash (21%), rhinitis (20%), diarrhea (20%), fever (18%), pneumonia (15%), gastroenteritis (11%), abdominal pain (10%), and anemia (7%). Treatment-emergent grades 3 to 4 laboratory abnormalities were experienced by 9% of pediatric subjects, including elevated amylase ( $>2 \times \text{ULN}$ ) (n=4), decreased neutrophils ( $<750/\text{mm}^3$ ) (n=3), elevated ALT ( $>5 \times \text{ULN}$ ) (n=2), elevated CPK ( $>4 \times \text{ULN}$ ) (n=2) and one subject each with elevated bilirubin ( $>3 \times \text{ULN}$ ), elevated GGT ( $>10 \times \text{ULN}$ ), elevated lipase ( $>2.5 \times \text{ULN}$ ), decreased hemoglobin ( $<7 \text{ g/dL}$ ), and decreased glucose ( $<40 \text{ mg/dL}$ ).

## 7 DRUG INTERACTIONS

The potential for drug interactions with emtricitabine has been studied in combination with zidovudine, indinavir, stavudine, famciclovir, and tenofovir DF. There were no clinically significant drug interactions for any of these drugs. Drug interactions trials are described elsewhere in the labeling [See Clinical Pharmacology (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Pregnancy Category B*

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose. There are, however, no adequate and well-controlled trials in pregnant women. Because animal reproduction studies are not always predictive of human response, emtricitabine should be used during pregnancy only if clearly needed.

*Antiretroviral Pregnancy Registry:* To monitor fetal outcomes of pregnant women exposed to emtricitabine, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

### 8.3 Nursing Mothers

**Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.** Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving emtricitabine.**

### 8.4 Pediatric Use

The safety and efficacy of emtricitabine in patients between 3 months and 21 years of age is supported by data from three open-label, nonrandomized clinical trials in which emtricitabine was administered to 169 HIV-1 infected treatment-naïve and experienced (defined as virologically suppressed on a lamivudine containing regimen for which emtricitabine was substituted for lamivudine) subjects [*See Clinical Studies(14.3)*].

The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-1 positive mothers [*See Clinical Studies (14.3)*]. All neonates were HIV-1 negative at the end of the trial; the efficacy of emtricitabine in preventing or treating HIV-1 could not be determined.

### 8.5 Geriatric Use

Clinical trials of emtricitabine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### 8.6 Patients with Impaired Renal Function

It is recommended that the dose or dosing interval for emtricitabine be modified in patients with creatinine clearance less than 50 mL/min or in patients who require dialysis [*See Dosage and Administration (2.5)*].

## 10 OVERDOSAGE

There is no known antidote for emtricitabine. Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology trial, single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported.

The effects of higher doses are not known. If overdose occurs, the patient should be monitored for signs of toxicity and standard supportive treatment applied as necessary.

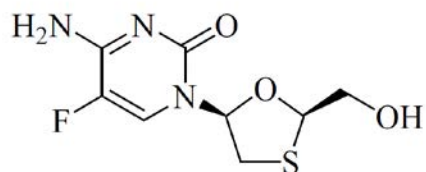
Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

## 11 DESCRIPTION

Emtricitabine is a synthetic nucleoside analog with activity against human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.

The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

It has a molecular formula of C<sub>8</sub>H<sub>10</sub>FN<sub>3</sub>O<sub>3</sub>S and a molecular weight of 247.24. It has the following structural formula:



Emtricitabine is an almost white crystalline powder with a solubility of approximately 112 mg/mL in water at 25°C. The log P for emtricitabine is -0.43 and the pKa is 2.65.

Emtricitabine is available as capsules.

Emtricitabine capsules are for oral administration. Each capsule contains 200 mg of emtricitabine and the inactive ingredients are crospovidone Type A, magnesium stearate, microcrystalline cellulose and povidone. The hard gelatin capsule shell contains FD & C Blue 2, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are printed with TekPrint™ SW-9008 Black Ink containing shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, and potassium hydroxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Emtricitabine is an antiviral drug [*See Clinical Pharmacology (12.4)*].

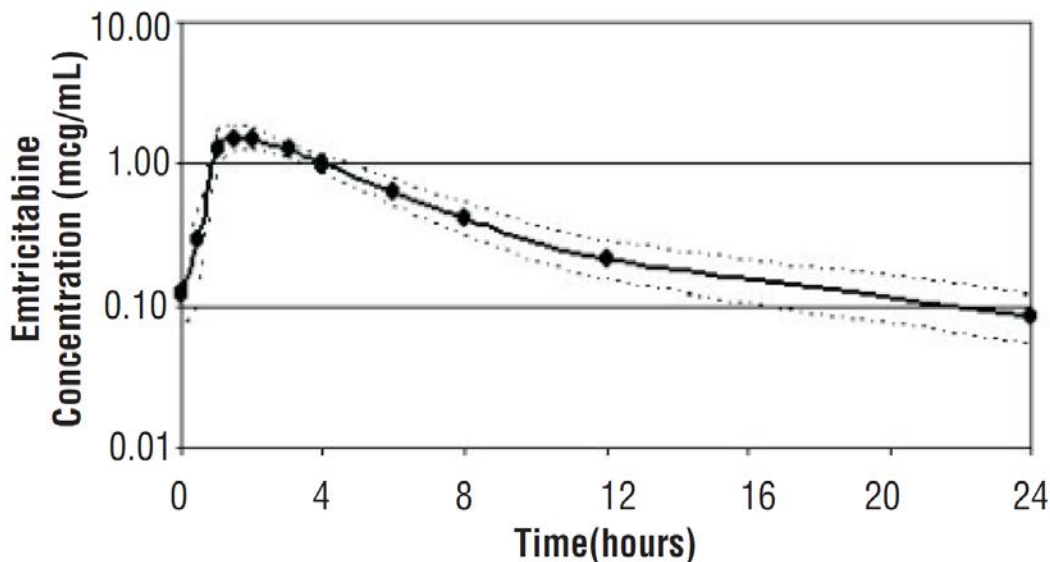
### 12.3 Pharmacokinetics

## Adults

The pharmacokinetics of emtricitabine were evaluated in healthy subjects and HIV-1-infected subjects. Emtricitabine pharmacokinetics are similar between these populations.

Figure 1 shows the mean steady-state plasma emtricitabine concentration-time profile in 20 HIV-1-infected subjects receiving emtricitabine capsules.

**Figure 1 Mean ( $\pm$  95% CI) Steady-State Plasma Emtricitabine Concentrations in HIV-1 Infected Adults (N=20)**



## Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration, with peak plasma concentrations occurring at 1 to 2 hours postdose. Following multiple dose oral administration of emtricitabine capsules to 20 HIV-1 infected subjects, the (mean  $\pm$  SD) steady-state plasma emtricitabine peak concentration ( $C_{max}$ ) was  $1.8 \pm 0.7$  mcg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was  $10 \pm 3.1$  mcg·hr/mL. The mean steady-state plasma trough concentration at 24 hours postdose was  $0.09$  mcg/mL. The mean absolute bioavailability of emtricitabine capsules was 93%, while the mean absolute bioavailability of emtricitabine oral solution was 75%. The relative bioavailability of emtricitabine oral solution was approximately 80% of emtricitabine capsules.

The multiple dose pharmacokinetics of emtricitabine are dose proportional over a dose range of 25 to 200 mg.

## Distribution

*In vitro* binding of emtricitabine to human plasma proteins was less than 4% and independent of concentration over the range of 0.02 to 200 mcg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1 and the mean semen to plasma drug concentration ratio was ~4.

### Metabolism

*In vitro* studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of <sup>14</sup>C-emtricitabine, complete recovery of the dose was achieved in urine (~86%) and feces (~14%). Thirteen percent (13%) of the dose was recovered in urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

### Elimination

The plasma emtricitabine half-life is approximately 10 hours. The renal clearance of emtricitabine is greater than the estimated creatinine clearance, suggesting elimination by both glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

### **Effects of Food on Oral Absorption**

Emtricitabine capsules and oral solution may be taken with or without food. Emtricitabine systemic exposure (AUC) was unaffected while  $C_{max}$  decreased by 29% when emtricitabine capsules were administered with food (an approximately 1000 kcal high-fat meal). Emtricitabine systemic exposure (AUC) and  $C_{max}$  were unaffected when 200 mg emtricitabine oral solution was administered with either a high-fat or low-fat meal.

### **Specific Populations**

#### Race, Gender

The pharmacokinetics of emtricitabine were similar in adult male and female subjects, and no pharmacokinetic differences due to race have been identified.

#### Pediatric Patients

The pharmacokinetics of emtricitabine at steady state were determined in 77 HIV-1 infected pediatric subjects, and the pharmacokinetic profile was characterized in four age groups (Table 6). The emtricitabine exposure achieved in pediatric subjects receiving a daily dose of 6 mg/kg up to a maximum of 240 mg oral solution or a 200 mg capsule is similar to exposures achieved in adult subjects receiving a once-daily dose of 200 mg.

The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-1 positive mothers. Each mother received prenatal and intrapartum combination antiretroviral therapy.

Neonates received up to 6 weeks of zidovudine prophylactically after birth. The neonates were administered two short courses of emtricitabine oral solution (each 3 mg/kg once daily × 4 days) during the first 3 months of life. The AUC observed in neonates who received a daily dose of 3 mg/kg of emtricitabine was similar to the AUC observed in pediatric subjects aged 3 months to 17 years who received a daily dose of emtricitabine as a 6 mg/kg oral solution up to 240 mg or as a 200 mg capsule (Table 6).

**Table 6 Mean ± SD Pharmacokinetic Parameters by Age Groups for Pediatric Subjects and Neonates Receiving Emtricitabine Capsules or Oral Solution**

	HIV-1-exposed Neonates	HIV-1-infected Pediatric Subjects			
Age	0 to 3 mo (N=20) <sup>a</sup>	3 to 24 mo (N=14)	25 mo to 6 yr (N=19)	7 to 12yr (N=17)	13 to 17 yr (N=27)
Formulation					
Capsule (n)	0	0	0	10	26
Oral Solution (n)	20	14	19	7	1
Dose (mg/kg) <sup>b</sup>	3.1 (2.9 to 3.4)	6.1(5.5 to 6.8)	6.1 (5.6 to 6.7)	5.6 (3.1 to 6.6)	4.4 (1.8 to 7)
C <sub>max</sub> (mcg/mL)	1.6 ± 0.6	1.9 ± 0.6	1.9 ± 0.7	2.7 ± 0.8	2.7 ± 0.9
AUC (mcg·hr/mL)	11 ± 4.2	8.7 ± 3.2	9 ± 3	12.6 ± 3.5	12.6 ± 5.4
T <sub>1/2</sub> (hr)	12.1 ± 3.1	8.9 ± 3.2	11.3 ± 6.4	8.2 ± 3.2	8.9 ± 3.3

a. Two pharmacokinetic evaluations were conducted in 20 neonates over the first 3 months of life. Median (range) age of infant on day of pharmacokinetic evaluation was 26 (5 to 81) days.

b. Mean (range).

### Geriatric Patients

The pharmacokinetics of emtricitabine have not been fully evaluated in the elderly.

### Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine are altered in subjects with renal impairment [*See Warnings and Precautions (5.3)*]. In adult subjects with creatinine clearance less than 50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C<sub>max</sub> and AUC of emtricitabine were increased due to a reduction in renal clearance (Table 7). It is recommended that the dosing interval for emtricitabine be modified in adult patients with creatinine clearance less than 50 mL/min or in adult patients with ESRD who require dialysis [*See Dosage and*



Administration (2.5)]. The effects of renal impairment on emtricitabine pharmacokinetics in pediatric patients are not known.

**Table 7 Mean ± SD Pharmacokinetic Parameters in Adult Subjects with Varying Degrees of Renal Function**

<b>Creatinine Clearance (mL/min)</b>	<b>&gt;80 (N=6)</b>	<b>50 to 80 (N=6)</b>	<b>30 to 49 (N=6)</b>	<b>&lt;30 (N=5)</b>	<b>ESRD<sup>a</sup> &lt;30 (N=5)</b>
Baseline creatinine clearance (mL/min)	107 ± 21	59.8 ± 6.5	40.9 ± 5.1	22.9 ± 5.3	8.8 ± 1.4
C <sub>max</sub> (mcg/mL)	2.2 ± 0.6	3.8 ± 0.9	3.2 ± 0.6	2.8 ± 0.7	2.8 ± 0.5
AUC (mcg·hr/mL)	11.8 ± 2.9	19.9 ± 1.2	25.1 ± 5.7	33.7 ± 2.1	53.2 ± 9.9
CL/F (mL/min)	302 ± 94	168 ± 10	138 ± 28	99 ± 6	64 ± 12
CLr (mL/min)	213 ± 89	121 ± 39	69 ± 32	30 ± 11	NA <sup>b</sup>

a. ESRD subjects requiring dialysis

b. NA = Not Applicable

Hemodialysis: Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

#### Patients with Hepatic Impairment

The pharmacokinetics of emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not metabolized by liver enzymes, so the impact of liver impairment should be limited.

#### **Assessment of Drug Interactions**

At concentrations up to 14-fold higher than those observed *in vivo*, emtricitabine did not inhibit *in vitro* drug metabolism mediated by any of the following human CYP isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Emtricitabine did not inhibit the enzyme responsible for glucuronidation (uridine-5'-disphosphoglucuronyl transferase). Based on the results of these *in vitro* experiments and the known elimination pathways of emtricitabine, the potential for CYP-mediated interactions involving emtricitabine with other medicinal products is low.

Emtricitabine has been evaluated in healthy volunteers in combination with tenofovir DF, zidovudine, indinavir, famciclovir, and stavudine. Tables 8 and 9 summarize the

pharmacokinetic effects of coadministered drug on emtricitabine pharmacokinetics and effects of emtricitabine on the pharmacokinetics of coadministered drug.

**Table 8 Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug<sup>a</sup>**

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters <sup>b</sup> (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↑20 (↑ 12 to ↑29)
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↔	↔	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	NA
Famciclovir	500 x 1	200 x 1	12	↔	↔	NA
Stavudine	40 x 1	200 x 1	6	↔	↔	NA

a. All interaction trials conducted in healthy volunteers.

b. ↑= Increase; ↔ = No Effect; NA = Not Applicable

**Table 9 Drug Interactions: Change in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine<sup>a</sup>**

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters <sup>b</sup> (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
Tenofovir DF	300 once daily x 7 days	200 once daily x 7 days	17	↔	↔	↔
Zidovudine	300 twice daily x 7 days	200 once daily x 7 days	27	↑ 17 (↑ 0 to ↑38)	↑13 (↑ 5 to ↑ 20)	↔
Indinavir	800 x 1	200 x 1	12	↔	↔	NA
Famciclovir	500 x 1	200 x 1	12	↔	↔	NA

Stavudine	40 × 1	200 × 1	6	↔	↔	NA
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a. All interaction trials conducted in healthy volunteers.

b. ↑= Increase; ↔ = No Effect; NA = Not Applicable

## 12.4 Microbiology

### Mechanism of Action

Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase  $\alpha$ ,  $\beta$ ,  $\epsilon$ , and mitochondrial DNA polymerase  $\gamma$ .

### Antiviral Activity

The antiviral activity in cell culture of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration ( $EC_{50}$ ) value for emtricitabine was in the range of 0.0013 to 0.64  $\mu$ M (0.0003 to 0.158 mcg/mL). In drug combination trials of emtricitabine with nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G ( $EC_{50}$  values ranged from 0.007 to 0.075  $\mu$ M) and showed strain-specific activity against HIV-2 ( $EC_{50}$  values ranged from 0.007 to 1.5  $\mu$ M).

The *in vivo* activity of emtricitabine was evaluated in two clinical trials in which 101 subjects were administered 25 to 400 mg a day of emtricitabine as monotherapy for 10 to 14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1 RNA of 1.3  $\log_{10}$  at a dose of 25 mg once daily and 1.7  $\log_{10}$  to 1.9  $\log_{10}$  at a dose of 200 mg once daily or twice daily.

### Resistance

Emtricitabine-resistant isolates of HIV-1 have been selected in cell culture and *in vivo*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a substitution in the HIV-1 reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

Emtricitabine-resistant isolates of HIV-1 have been recovered from some subjects treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical trial of

treatment-naïve subjects treated with emtricitabine, didanosine, and efavirenz [See *Clinical Studies (14.1)*], viral isolates from 37.5% of subjects with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I substitutions in the HIV-1 reverse transcriptase gene.

In a clinical trial of treatment-naïve subjects treated with either emtricitabine, VIREAD, and efavirenz or zidovudine/lamivudine and efavirenz [See *Clinical Studies (14.1)*], resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to emtricitabine and lamivudine, was observed in 2/19 analyzed subject isolates in the emtricitabine + VIREAD group and in 10/29 analyzed subject isolates in the lamivudine/zidovudine group. Through 144 weeks of Study 934, no subjects have developed a detectable K65R substitution in their HIV-1 as analyzed through standard genotypic analysis.

### **Cross Resistance**

Cross-resistance among certain nucleoside analog reverse transcriptase inhibitors has been recognized. Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity in cell culture to didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to emtricitabine.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), or mouse lymphoma or mouse micronucleus assays.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

## 14 CLINICAL STUDIES

### 14.1 Treatment-Naïve Adult Patients

#### Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter clinical trial comparing Emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve subjects. From Weeks 96 to 144 of the trial, subjects received emtricitabine/tenofovir DF fixed-dose combination with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Subjects had a mean age of 38 years (range 18 to 80); 86% were male, 59% were Caucasian, and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm<sup>3</sup> (range 2 to 1191) and median baseline plasma HIV-1 RNA was 5.01 log<sub>10</sub> copies/mL (range 3.56 to 6.54). Subjects were stratified by baseline CD4+ cell count (< or ≥200 cells/mm<sup>3</sup>); 41% had CD4+ cell counts <200 cells/mm<sup>3</sup> and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 10.

**Table 10 Outcomes of Randomized Treatment at Week 48 and 144 (Study 934)**

Outcomes	Week 48		Week 144	
	Emtricitabine +TDF +EFV (N=244)	AZT/3TC +EFV (N=243)	Emtricitabine +TDF +EFV (N=227) <sup>a</sup>	AZT/3TC +EFV (N=229) <sup>a</sup>
Responder <sup>b</sup>	84%	73%	71%	58%
Virologic failure <sup>c</sup>	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death	<1%	1%	1%	1%
Discontinued due to adverse event	4%	9%	5%	12%
Discontinued for other reasons <sup>d</sup>	10%	14%	20%	22%

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue in the trial after Week 48 or Week 96 were excluded from analysis.

b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.

c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.

d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

Through Week 48, 84%, and 73% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4<sup>+</sup> cell count was 190 cells/mm<sup>3</sup> in the emtricitabine + tenofovir DF group and 158 cells/mm<sup>3</sup> in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm<sup>3</sup> at Week 144).

Through 48 weeks, 7 subjects in the emtricitabine + tenofovir DF group and 5 subjects in the zidovudine/lamivudine group experienced a new CDC Class C event (10 and 6 subjects through 144 weeks).

### Study 301A

Study 301A was a 48-week double-blind, active-controlled, multicenter clinical trial comparing emtricitabine (200 mg once daily) administered in combination with didanosine, and efavirenz versus stavudine, didanosine and efavirenz in 571 antiretroviral naïve adult subjects. Subjects had a mean age of 36 years (range 18 to 69); 85% were male, 52% Caucasian, 16% African-American, and 26% Hispanic. Subjects had a mean baseline CD4<sup>+</sup> cell count of 318 cells/mm<sup>3</sup> (range 5 to 1317) and median baseline plasma HIV-1 RNA of 4.9 log<sub>10</sub> copies/mL (range 2.6 to 7). Thirty-eight percent of subjects had baseline viral loads >100,000 copies/mL and 31% had CD4<sup>+</sup> cell counts <200 cells/mL. Treatment outcomes are presented in Table 11.

**Table 11 Outcomes of Randomized Treatment at Week 48 (Study 301A)**

<b>Outcomes</b>	<b>Emtricitabine + Didanosine + Efavirenz (N=286)</b>	<b>Stavudine + Didanosine + Efavirenz (N=285)</b>
Responder <sup>a</sup>	81% (78%)	68% (59%)
Virologic Failure <sup>b</sup>	3%	11%
Death	0%	<1%
Discontinuation Due to Adverse Event	7%	13%
Discontinuation for Other Reasons <sup>c</sup>	9%	8%

- Subjects achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48.
- Includes subjects who failed to achieve virologic suppression or rebounded after achieving virologic suppression.
- Includes lost to follow-up, subject withdrawal, non-compliance, protocol violation, and other reasons.

The mean increase from baseline in CD4<sup>+</sup> cell count was 168 cells/mm<sup>3</sup> for the emtricitabine arm and 134 cells/mm<sup>3</sup> for the stavudine arm.

Through 48 weeks, in the emtricitabine group, 5 subjects (1.7%) experienced a new CDC Class C event compared to 7 subjects (2.5%) in the stavudine group.

## 14.2 Treatment-Experienced Adult Patients

### Study 303

Study 303 was a 48 week, open-label, active-controlled multicenter clinical trial comparing emtricitabine (200 mg once daily) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 adult subjects who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to trial entry and had HIV-1 RNA  $\leq$ 400 copies/mL.

Subjects were randomized 1:2 to continue therapy with lamivudine (150 mg twice daily) or to switch to emtricitabine (200 mg once daily). All subjects were maintained on their stable background regimen. Subjects had a mean age of 42 years (range 22 to 80); 86% were male, 64% Caucasian, 21% African-American, and 13% Hispanic. Subjects had a mean baseline CD4<sup>+</sup> cell count of 527 cells/mm<sup>3</sup> (range 37 to 1909), and a median baseline plasma HIV-1 RNA of 1.7 log<sub>10</sub> copies/mL (range 1.7 to 4).

The median duration of prior antiretroviral therapy was 27.6 months. Treatment outcomes are presented in Table 12.

**Table 12 Outcomes of Randomized Treatment at Week 48 (Study 303)**

<b>Outcomes</b>	<b>Emtricitabine + ZDV/d4T + NNRTI/PI (N=294)</b>	<b>Lamivudine + ZDV/d4T + NNRTI/PI (N=146)</b>
Responder <sup>a</sup>	77% (67%)	82% (72%)
Virologic Failure <sup>b</sup>	7%	8%
Death	0%	<1%
Discontinuation Due to Adverse Event	4%	0%
Discontinuation for Other Reasons <sup>c</sup>	12%	10%

a. Subjects achieved and maintained confirmed HIV RNA <400 copies/mL (<50 copies/mL) through Week 48.

b. Includes subjects who failed to achieve virologic suppression or rebounded after achieving virologic suppression.

c. Includes lost to follow-up, subject withdrawal, non-compliance, protocol violation, and other reasons.

The mean increase from baseline in CD4<sup>+</sup> cell count was 29 cells/mm<sup>3</sup> for the emtricitabine arm and 61 cells/mm<sup>3</sup> for the lamivudine arm.

Through 48 weeks, in the emtricitabine group 2 subjects (0.7%) experienced a new CDC Class C event compared to 2 subjects (1.4%) in the lamivudine group.

### 14.3 Pediatric Patients

In three open-label, nonrandomized clinical trials, emtricitabine was administered to 169 HIV-1 infected treatment-naïve and experienced (defined as virologically suppressed on a lamivudine containing regimen for which emtricitabine was substituted for lamivudine) subjects between 3 months and 21 years of age. Subjects received once-daily emtricitabine oral solution (6 mg/kg to a maximum of 240 mg/day) or emtricitabine capsules (a single 200 mg capsule once daily) in combination with at least two other antiretroviral agents.

Subjects had a mean age of 7.9 years (range 0.3 to 21); 49% were male, 15% Caucasian, 61% Black, and 24% Hispanic. Subjects had a median baseline HIV-1 RNA of 4.6 log<sub>10</sub> copies/mL (range 1.7 to 6.4) and a mean baseline CD4<sup>+</sup> cell count of 745 cells/mm<sup>3</sup> (range 2 to 2650). Through 48 weeks of therapy, the overall proportion of subjects who achieved and sustained an HIV-1 RNA <400 copies/mL was 86%, and <50 copies/mL was 73%. The mean increase from baseline in CD4<sup>+</sup> cell count was 232 cells/mm<sup>3</sup> (-945, +1512). The adverse reaction profile observed during these clinical trials was similar to that of adult subjects, with the exception of the occurrence of anemia and higher frequency of hyperpigmentation in children [*See Adverse Reactions (6)*].

The pharmacokinetics of emtricitabine were studied in 20 neonates born to HIV-1 positive mothers. Each mother received prenatal and intrapartum combination antiretroviral therapy. Neonates received up to 6 weeks of zidovudine prophylactically after birth. The neonates were administered two short courses of emtricitabine oral solution (each 3 mg/kg once daily × 4 days) during the first 3 months of life. Emtricitabine exposures in neonates were similar to the exposures achieved in subjects aged 3 months to 17 years [*See Clinical Pharmacology (12.3)*]. During the two short dosing periods on emtricitabine there were no safety issues identified in the treated neonates. All neonates were HIV-1 negative at the end of the trial; the efficacy of emtricitabine in preventing or treating HIV-1 could not be determined.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### *Capsules*

Size '1' Hard gelatin Capsule with a light blue opaque cap and white opaque body, printed with 'M' in black on the cap and '18' in black on the body, filled with off white granular powder of:

- |                                       |                  |
|---------------------------------------|------------------|
| – Bottle of 30                        | NDC 42571-139-30 |
| – Carton of 5 x 10 Unit-dose Capsules | NDC 42571-139-24 |



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

## **17 PATIENT COUNSELING INFORMATION**

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

Inform patients that:

- Emtricitabine is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using emtricitabine.

Advise patients to avoid doing things that can spread HIV to others.

- **Do not 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.**
- **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 semen, vaginal secretions, or blood.
- **Do not breastfeed.** Emtricitabine is secreted in breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Inform patients that:

- The long-term effects of emtricitabine are unknown.
- Emtricitabine capsules and oral solution are for oral ingestion only.
- It is important to take emtricitabine with combination therapy on a regular dosing schedule to avoid missing doses.
- Severe acute exacerbations of Hepatitis B have been reported in patients who are coinfecting with HBV and HIV-1 and have discontinued emtricitabine [*See Warnings and Precautions (5.1)*].
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with emtricitabine should be suspended in any patient who develops clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity [*See Warnings and Precautions (5.2)*].
- Emtricitabine should not be coadministered with ATRIPLA, COMPLERA, DESCOVY, GENVOYA, ODEFSEY, STRIBILD, or TRUVADA; or with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Triumeq (abacavir sulfate/dolutegravir/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine) [*See Warnings and Precautions (5.3)*].
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine [*See Warnings and Precautions (5.5)*].

Manufactured by:  
**Micro Labs Limited**

Goa-403 722, India.

Manufactured for:

**Micro Labs USA Inc.**  
Basking Ridge, NJ 07920

**Revised: 08/2018**

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**PATIENT INFORMATION**  
**EMTRICITABINE CAPSULES**

Generic name: emtricitabine (em tri SIT uh bean)

Read the Patient Information that comes with emtricitabine capsules before you start using it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

You should stay under a healthcare provider's care when taking emtricitabine capsules. **Do not change or stop your medicine without first talking with your healthcare provider.** Talk to your healthcare provider or pharmacist if you have any questions about emtricitabine capsules.

**What is the most important information I should know about emtricitabine capsules?**

**If you are also infected with the Hepatitis B Virus (HBV),** you need close medical follow-up for several months after stopping treatment with emtricitabine capsules. Follow-up includes medical exams and blood tests to check for HBV that is getting worse. **Patients with HBV infection who take emtricitabine capsules and then stop it may get "flare-ups" of their hepatitis. A "flare-up" is when the disease suddenly returns in a worse way than before.**

**What are emtricitabine capsules?**

Emtricitabine capsules are a type of medicine called an HIV-1 (human immunodeficiency virus) nucleoside reverse transcriptase inhibitor (NRTI). Emtricitabine capsules are always used with other anti-HIV-1 medicines to treat people with HIV-1 infection. **Emtricitabine capsules are for adults and children, but has not been studied fully in adults over age 65.**

HIV infection destroys CD4+ T cells, which are important to the immune system. The immune system helps fight infection. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

Emtricitabine helps to block HIV-1 reverse transcriptase, a chemical in your body (enzyme) that is needed for HIV-1 to multiply. Emtricitabine may lower the amount of HIV-1 in the blood (viral load). Emtricitabine may also help to increase the number of T cells, called CD4+ cells. Lowering the amount of HIV-1 in the blood lowers the chance of death or infections that happen when your immune system is weak (opportunistic infections).

**Emtricitabine capsules does not cure HIV-1 infection or AIDS.** The long-term effects of emtricitabine capsules are not known at this time. People taking emtricitabine capsules may still get opportunistic infections or other conditions that happen with HIV-1 infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. **It is very important that you see your healthcare provider regularly while taking emtricitabine capsules.**

## Who should not take emtricitabine capsules?

Do not take emtricitabine capsules if you are allergic to emtricitabine capsules or any of its ingredients. The active ingredient is emtricitabine. See the end of this leaflet for a complete list of ingredients.

Do not take emtricitabine capsules if you are already taking ATRIPLA<sup>®</sup>, COMPLERA<sup>®</sup>, DESCOVY<sup>®</sup>, GENVOYA<sup>®</sup>, ODEFSEY<sup>®</sup>, STRIBILD<sup>®</sup>, TRUVADA<sup>®</sup>, Combivir, Epivir, Epivir-HBV, Epzicom, Triumeq, or Trizivir because these medicines contain the same or similar active ingredients.

## What should I tell my healthcare provider before taking emtricitabine capsules?

### Tell your healthcare provider

**If you are pregnant or planning to become pregnant.** We do not know if emtricitabine capsules can harm your unborn child. You and your healthcare provider will need to decide if emtricitabine capsules are right for you. If you use emtricitabine capsules while you are pregnant, talk to your healthcare provider about how you can be on the emtricitabine Antiviral Pregnancy Registry.

**If you are breastfeeding.** You should not breastfeed if you are HIV-positive because of the chance of passing the HIV virus to your baby. Also, emtricitabine can pass into your breast milk and it is not known if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.

**If you have kidney problems.** You may need to take emtricitabine capsules less often.

**If you have any liver problems including Hepatitis B Virus infection.**

**Tell your healthcare provider about all your medical conditions.**

**Tell your healthcare provider about all the medicines you take** such as prescription and nonprescription medicines and dietary supplements. Keep a complete list of all the medicines that you take. Make a new list when medicines are added or stopped. Give copies of this list to all of your healthcare providers and pharmacist **every** time you visit or fill a prescription.

## How should I take emtricitabine capsules?

- Take emtricitabine capsules by mouth exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label.
  - Dosing in adults: The usual dose of emtricitabine capsules is 1 capsule once a day.
  - Dosing in children: The child's doctor will calculate the right dose of emtricitabine capsules based on the child's weight.
- Emtricitabine capsules are always used with other anti-HIV-1 medicines.
- Emtricitabine capsules may be taken with or without a meal. Food does not affect how emtricitabine capsules works.
- If you forget to take emtricitabine capsule, take it as soon as you remember that day. **Do not** take more than 1 dose of emtricitabine capsule in a day. **Do not** take 2 doses at the same time. Call your healthcare provider or pharmacist if you are not sure what to do. **It is important**

**that you do not miss any doses of emtricitabine capsules or your other anti-HIV-1 medicines.**

- When your emtricitabine capsule supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to emtricitabine and become harder to treat.
- Stay under a healthcare provider's care when taking emtricitabine capsules. Do not change your treatment or stop treatment without first talking with your healthcare provider.
- If you take too much emtricitabine capsules, call your local poison control center or emergency room right away.

### **What should I avoid while taking emtricitabine capsules?**

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades.**
- **Do not have any kind of sex without protection.** Always practice safer sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Emtricitabine can be passed to your baby in your breast milk. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

### **What are the possible side effects of emtricitabine capsules?**

**Emtricitabine capsules may cause the following serious side effects** (See "What is the most important information I should know about emtricitabine capsules?"):

**“flare-ups” of Hepatitis B Virus infection,** in which the disease suddenly returns in a worse way than before, can occur if you stop taking emtricitabine capsules. Emtricitabine capsule is not for the treatment of Hepatitis B Virus (HBV) infection.

**Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.

**Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark “tea-colored” urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effects of emtricitabine capsules used with other anti-HIV-1 medicines are headache, diarrhea, and nausea. Other side effects include allergic reaction, dizziness, sleeping problems, abnormal dreams, vomiting, indigestion, stomach pain, pain, weakness, and rash. Skin discoloration may also happen with emtricitabine.

There have been other side effects in patients taking emtricitabine capsules. However, these side effects may have been due to other medicines that patients were taking or to HIV-1 itself. Some of these side effects can be serious.

This list of side effects is **not** complete. If you have questions about side effects, ask your healthcare provider or pharmacist. You should report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

### **How do I store emtricitabine capsules?**

- Keep emtricitabine capsules and all other medicines out of reach of children.
- Store emtricitabine capsules at 25°C (77°F) excursions permitted to 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature].
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

### **General information about emtricitabine capsules:**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use emtricitabine capsules for a condition for which it was not prescribed. Do not give emtricitabine capsules to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about emtricitabine capsules. If you would like more information, talk with your doctor. You can ask your healthcare provider or pharmacist for information about emtricitabine capsules that is written for health professionals. For more information, you may also call 1-855-875-7814.

### **What are the ingredients of emtricitabine capsules?**

**Active Ingredient:** Emtricitabine

**Inactive Ingredients:** Crospovidone Type A, magnesium stearate, microcrystalline cellulose and povidone. The hard gelatin capsule shell contains FD & C Blue 2, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are printed with TekPrint™ SW-9008 Black Ink containing shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, and potassium hydroxide.

**Rx Only**

Manufactured by:  
**Micro Labs Limited**  
Goa-403 722, India.

Manufactured for:  
**Micro Labs USA Inc.**  
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