

Product Monograph

Pr Emtriva[®]

(Emtricitabine Capsules)

200 mg

Antiretroviral Agent

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Product Monograph for Emtriva® (Emtricitabine Capsules)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule 200 mg	None. <i>For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section</i>

INDICATIONS AND CLINICAL USE

EMTRIVA is indicated, in combination with other antiretroviral agents, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 48 weeks duration in antiretroviral-naïve patients and antiretroviral-treatment-experienced patients who were virologically suppressed on an HIV treatment regimen.

In antiretroviral-treatment-experienced patients, the use of EMTRIVA may be considered for adults with HIV strains that are expected to be susceptible to EMTRIVA as assessed by genotypic or phenotypic testing.

Geriatrics (>65 years of age):

Clinical studies of EMTRIVA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects (see **WARNINGS AND PRECAUTIONS, Geriatrics and DOSAGE AND ADMINISTRATION**).

Pediatrics:

EMTRIVA is not approved for use in patients < 18 years of age.

CONTRAINDICATIONS

EMTRIVA is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Lactic Acidosis and 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 emtricitabine and other antiretrovirals (see WARNINGS and PRECAUTIONS).

- **Post-Treatment Exacerbation of Hepatitis**

EMTRIVA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of EMTRIVA have not been established in patients coinfecting with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of antiretroviral therapy, including EMTRIVA. 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 and HBV and discontinue EMTRIVA. If appropriate, initiation of anti-hepatitis B therapy may be warranted (see WARNINGS and PRECAUTIONS).

General

EMTRIVA is a component of TRUVADA[®], ATRIPLA[®], COMPLERA[®] and STRIBILD[®]. EMTRIVA should not be coadministered with TRUVADA, ATRIPLA, COMPLERA or STRIBILD. Due to similarities between emtricitabine and lamivudine, EMTRIVA should not be coadministered with other drugs containing lamivudine such as COMBIVIR[®], 3TC[®], HEPTOVIR[®], KIVEXA[®] or TRIZIVIR[®].

Carcinogenesis and Mutagenesis

In long-term oral carcinogenicity studies of emtricitabine, no drug-related increase in tumor incidence was 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), mouse lymphoma or mouse micronucleus assays.

Endocrine and Metabolism

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 unknown. A causal relationship has not been established.

Hepatic

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 alone or in combination with 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 nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with EMTRIVA 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).

Immune

Immune Reconstitution: During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as MAC, CMV, PCP, and TB) which may necessitate further evaluation and treatment.

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

Renal

Emtricitabine is principally eliminated by the kidney. Reduction of the dosage of EMTRIVA is recommended for patients with impaired renal function (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions and DOSAGE AND ADMINISTRATION**).

Special Populations

Patients with HIV and Hepatitis B Virus Coinfection

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. EMTRIVA is not approved for the treatment of chronic HBV infection and the safety and efficacy of EMTRIVA have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of EMTRIVA. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who are co-infected with HIV and HBV and discontinue EMTRIVA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. 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. Because

animal reproduction studies are not always predictive of human response, EMTRIVA 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.

Nursing Women

HIV-infected mothers should not breast-feed their infants to avoid risking postnatal transmission of HIV. Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk at estimated neonatal concentrations 3 to 12 times higher than the emtricitabine IC_{50} but 3 to 12 times lower than the C_{min} achieved from oral administration of emtricitabine. Breast-feeding 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 transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving EMTRIVA.**

Geriatrics (>65 years of age)

Clinical studies of EMTRIVA 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 (see **WARNINGS AND PRECAUTIONS, Renal and DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials included headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical studies due to these events. All adverse events were reported with similar frequency in EMTRIVA and control treatment groups with the exception of skin discoloration which was reported with higher frequency in the EMTRIVA treated group. Skin discoloration, mainly manifested by hyperpigmentation on the palms and/or soles, was generally mild, asymptomatic and of little clinical significance. The mechanism is unknown.

In Study FTC-203, an open-label, uncontrolled study of 116 pediatric patients, anemia was observed with an incidence rate of 10% and hyperpigmentation was observed with an incidence of >10%.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

More than 2000 adult patients with HIV infection have been treated with EMTRIVA alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in Phase 1-3 clinical trials. Assessment of adverse reactions is based on data from studies 301A and 303 in which 571 treatment naïve (301A) and 440 treatment experienced (303) patients received EMTRIVA 200 mg (N=580) or comparator drug (N=431) for 48 weeks.

A summary of EMTRIVA treatment emergent clinical adverse events in studies 301A and 303 is provided in Table 1.

Table 1 Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in $\geq 3\%$ of EMTRIVA-Treated Patients in Either Study 301A or 303 (0–48 weeks)

Adverse Event	303		301A	
	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	EMTRIVA + 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%	24%
Digestive System				
Diarrhea	22%	19%	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%	3%	6%	3%
Nervous System				
Abnormal dreams	2%	<1%	11%	19%
Depressive disorders	6%	10%	9%	13%
Dizziness	4%	5%	25%	25%
Insomnia	7%	3%	16%	21%
Neuropathy/peripheral neuritis	4%	3%	4%	13%
Paresthesia	5%	6%	6%	12%
Respiratory				
Increased cough	14%	11%	14%	8%
Rhinitis	17%	12%	12%	10%
Skin				
Rash event ¹	16%	10%	32%	36%

1. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory abnormalities in these studies occurred with similar frequency in the EMTRIVA and comparator groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 2.

Table 2 Treatment-Emergent Grade 3/4 Laboratory Abnormalities Reported in ≥1% of EMTRIVA-Treated Patients in Either Study 301A or 303

Number of Patients Treated	303		301A	
	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	EMTRIVA + didanosine + efavirenz (N=286)	Stavudine + didanosine + efavirenz (N=285)
Percentage with grade 3/4 laboratory abnormality	30%	27%	31%	37%
ALT (>5.0 x ULN ¹)	2%	1%	4%	5%
AST (>5.0 x ULN)	3%	1%	5%	8%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine kinase (>4.0 x ULN)	11%	13%	10%	9%
Neutrophils (<750 mm ³)	5%	3%	5%	7%
Pancreatic amylase (>2.0 x ULN)	2%	2%	<1%	1%
Serum amylase (>2.0 x ULN)	2%	2%	4%	9%
Serum glucose (<40 or >250 mg/dL)	2%	2%	3%	3%
Serum lipase (>2.0 x ULN)	1%	1%	1%	2%

1. ULN = Upper limit of normal

Cases of spontaneously resolving grade 2, 3, or 4 neutropenia events occurred in 12/286 patients (4%) on FTC-containing antiretroviral regimen in FTC-301A and 2/294 patients (<1%) in FTC-303 where a relationship to emtricitabine could not be ruled out.

Post-Market Adverse Drug Reactions

The following adverse experiences have been reported in post-marketing experience without regard to causality. Because these events are voluntarily reported from a population of unknown size, estimates of frequency cannot be made.

Blood and lymphatic system disorders: Thrombocytopenia

Gastrointestinal disorders: Pancreatitis

General disorders and administration site conditions: Pyrexia

Metabolism and nutrition disorders: Lactic acidosis

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral

therapy an inflammatory reaction to infectious pathogens (active or inactive) may arise (see **WARNINGS and PRECAUTIONS**).

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 450 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 CYP450 mediated interactions involving emtricitabine with other medicinal products is low.

Emtricitabine has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (DF), zidovudine, indinavir, famciclovir, and stavudine. Table 3 and Table 4 summarize the pharmacokinetic effects of coadministered drug on emtricitabine pharmacokinetics and effects of emtricitabine on the pharmacokinetics of coadministered drug.

Table 3 Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Coadministered Drug¹

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Emtricitabine Pharmacokinetic Parameters ² (90% CI)		
				C _{max}	AUC	C _{min}
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

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ↔ = No Effect; NA = Not Applicable

Table 4 Drug Interactions: Change in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine¹

Coadministered Drug	Dose of Coadministered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters ² (90% CI)		
				C _{max}	AUC	C _{min}
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 x 1	200 x 1	6	↔	↔	NA

1. All interaction studies conducted in healthy volunteers.
2. ↑ = Increase; ↓ = Decrease; ↔ = No Effect; NA = Not Applicable

Drug-Food Interactions

Emtriva can be taken with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Effects of Food on Oral Absorption**).

Drug-Herb Interactions

Interactions of Emtriva with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

For adults 18 years of age and older, the dose of EMTRIVA is 200 mg once daily taken orally with or without food.

Dose Adjustment in Patients with Renal Impairment

Significantly increased drug exposures were seen when EMTRIVA was administered to patients with renal impairment, (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**). Therefore, the dosing interval of EMTRIVA should be adjusted in patients with baseline creatinine clearance <50 mL/min using the following guidelines (see Table 5). The safety and effectiveness of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

Table 5 Dosing Interval Adjustment in Patients with Renal Impairment

	Creatinine Clearance (mL/min)			
	≥50	30–49	15–29	<15 (including patients requiring hemodialysis) ¹
Recommended Dose and Dosing Interval	200 mg every 24 hours	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours

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

OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

There is no known antidote for EMTRIVA. Limited clinical experience is available at doses higher than the therapeutic dose of EMTRIVA. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. 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), however, a single treatment does not significantly affect emtricitabine C_{max} or AUC. It is not known whether emtricitabine can be removed by peritoneal dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Emtricitabine, a synthetic nucleoside analog of cytosine, 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 α , β , ϵ and mitochondrial DNA polymerase γ .

Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 μ M) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μ M).

Pharmacodynamics

The in vivo activity of emtricitabine was evaluated in two clinical trials in which 101 patients were administered 25 to 400 mg a day of EMTRIVA as monotherapy for 10 to 14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1

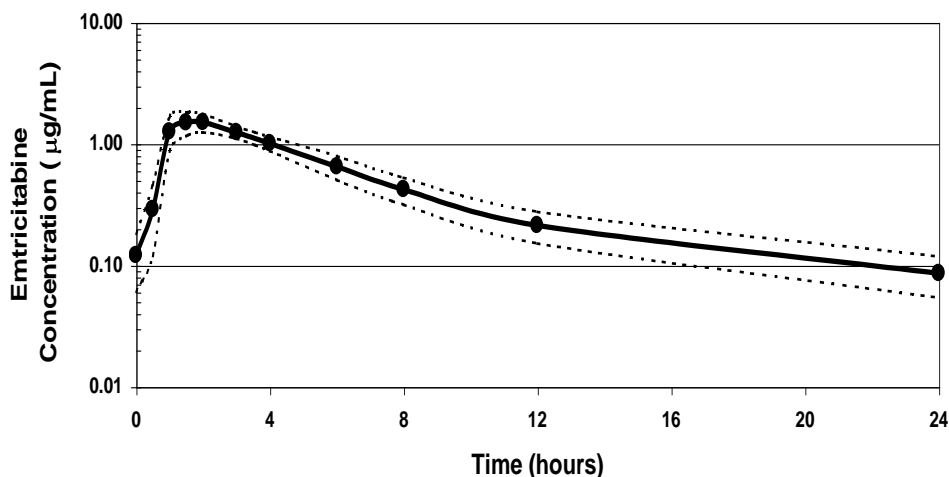
RNA of 1.3 log₁₀ at a dose of 25 mg QD and 1.7 log₁₀ to 1.9 log₁₀ at a dose of 200 mg QD or BID.

Pharmacokinetics

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

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

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



Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of EMTRIVA to 20 HIV-infected subjects, the (mean \pm SD) steady-state plasma emtricitabine peak concentration (C_{max}) was 1.8 ± 0.7 µg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ± 3.1 µg·hr/mL. The mean steady state plasma trough concentration at 24 hours post-dose was 0.09 µg/mL. The mean absolute bioavailability of EMTRIVA was 93%.

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

Effects of Food on Oral Absorption

EMTRIVA may be taken with or without food. Emtricitabine systemic exposure (AUC) was unaffected while C_{max} decreased by 29% when EMTRIVA was administered with food (an approximately 1000 kcal high-fat meal).

Distribution

In vitro binding of emtricitabine to human plasma proteins was <4% and independent of concentration over the range of 0.02–200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

Metabolism

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of ¹⁴C-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.

Special Populations and Conditions

Gender and Race

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

Pediatrics

EMTRIVA is not approved for use in patients < 18 years of age.

Geriatric Use (>65 years of age)

Pharmacokinetic data are not available in the elderly.

Renal Insufficiency

The pharmacokinetics of emtricitabine are altered in patients with renal impairment (see **WARNINGS AND PRECAUTIONS**). In patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max} and AUC of emtricitabine were increased due to a reduction in renal clearance (Table 6). It is recommended that the dosing interval for EMTRIVA be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis (see **DOSAGE AND ADMINISTRATION**).

Table 6 Mean ± SD Pharmacokinetic Parameters in Patients with Varying Degrees of Renal Function

Creatinine Clearance (mL/min)	>80 (N=6)	50–80 (N=6)	30–49 (N=6)	<30 (N=5)	ESRD¹ <30 (N=5)
Baseline creatinine clearance (mL/min)	107 ± 21	59.8 ± 6.5	40.9 ± 5.1	22.9 ± 5.3	8.8 ± 1.4
C _{max} (µg/mL)	2.2 ± 0.6	3.8 ± 0.9	3.2 ± 0.6	2.8 ± 0.7	2.8 ± 0.5
AUC (µg·hr/mL)	11.8 ± 2.9	19.9 ± 1.1	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
CL _r (mL/min)	213 ± 89	121 ± 39	69 ± 32	30 ± 11	NA ²

1. ESRD patients requiring dialysis.
2. 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), but a single treatment does not significantly affect emtricitabine C_{max} or AUC. It is not known whether emtricitabine can be removed by peritoneal dialysis.

Hepatic Insufficiency

The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment, however, emtricitabine has not been shown to be metabolized by liver enzymes, so the impact of liver impairment is likely to be limited.

STORAGE AND STABILITY

Store EMTRIVA (emtricitabine) capsules at 15–30 °C (59–86 °F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

EMTRIVA is available as capsules each containing 200 mg of emtricitabine and the inactive ingredients, crospovidone, magnesium stearate, microcrystalline cellulose, and povidone. EMTRIVA 200 mg capsules are size 1 hard gelatin capsules with a blue cap and white body, printed with “200 mg” in black on the cap and “GILEAD” and the corporate logo in black on the body. EMTRIVA capsules are packaged in bottles of 30 capsules with induction sealed child-resistant closures.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance:

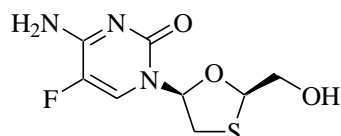
Common name: emtricitabine (USAN)

Chemical Name: 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

Molecular Formula: C₈H₁₀FN₃O₃S

Molecular Weight: 247.24 g/mol

Structural Formula:



Physicochemical Properties:

Physical Description: Emtricitabine is a white to off-white powder.

Solubility: The solubility of emtricitabine is approximately 112 mg/mL in water at 25 °C. The partition coefficient (log p) for emtricitabine is -0.43 and the pKa is 2.65.

CLINICAL TRIALS

Study Demographics, Trial Design and Results

Study 301A: EMTRIVA QD + Didanosine QD + Efavirenz QD Compared to Stavudine BID + Didanosine QD + Efavirenz QD

Study 301A was a 48 week double-blind, active-controlled multicenter study comparing EMTRIVA (200 mg QD) administered in combination with didanosine and efavirenz versus stavudine, didanosine and efavirenz in 571 antiretroviral naïve-patients. Patients had a mean age of 36 years (range 18–69), 85% were male, 52% Caucasian, 16% African-American and 26% Hispanic. Patients had a mean baseline CD4 cell count of 318 cells/mm³ (range 5–1317) and a median baseline plasma HIV RNA of 4.9 log₁₀ copies/mL (range 2.6–7.0). Thirty-eight percent of patients had baseline viral loads >100,000 copies/mL and 31% had CD4 cell counts <200 cells/mL. Treatment outcomes are presented in Table 7.

Table 7 Outcomes of Randomized Treatment at Week 48 (Study 301A)

Outcome at Week 48	EMTRIVA+ didanosine+ efavirenz (N=286)	Stavudine+ didanosine+ efavirenz (N=285)
Responder ¹	81% (78%)	68% (59%)
Virologic failure ²	3%	11%
Death	0%	<1%
Study discontinuation due to adverse event	7%	13%
Study discontinuation for other reasons ³	9%	8%

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

The mean increase from baseline in CD4 cell count was 168 cells/mm³ for the EMTRIVA arm and 134 cells/mm³ for the stavudine arm.

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

Study 303: EMTRIVA QD + Stable Background Therapy (SBT) Compared to Lamivudine BID + SBT

Study 303 was a 48 week, open-label, active-controlled multicenter study comparing EMTRIVA (200 mg QD) to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 patients who were on a lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry and had HIV-1 RNA ≤400 copies/mL.

Patients were randomized 1:2 to continue therapy with lamivudine (150 mg BID) or to switch to EMTRIVA (200 mg QD). All patients were maintained on their stable background regimen. Patients had a mean age of 42 years (range 22–80), 86% were male, 64% Caucasian, 21% African-American and 13% Hispanic. Patients had a mean baseline CD4 cell count of 527 cells/mm³ (range 37–1909), and a median baseline plasma HIV RNA of 1.7 log₁₀ copies/mL (range 1.7–4.0).

The median duration of prior antiretroviral therapy was 27.6 months. Treatment outcomes are presented in Table 8.

Table 8 Outcomes of Randomized Treatment at Week 48 (Study 303)

Outcome at Week 48	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)
Responder ¹	77% (67%)	82% (72%)
Virologic failure ²	7%	8%
Death	0%	<1%
Study discontinuation due to adverse event	4%	0%
Study discontinuation for other reasons ³	12%	10%

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

The mean increase from baseline in CD4 cell count was 29 cells/mm³ for the EMTRIVA arm and 61 cells/mm³ for the lamivudine arm. Through 48 weeks, in the EMTRIVA group 2 patients (0.7%) experienced a new CDC Class C event, compared to 2 patients (1.4%) in the lamivudine group.

Comparative Bioavailability Studies

An open-label, randomized, three-period crossover study was conducted in 17 male and 7 female volunteers to establish the bioequivalence of two dosage forms of emtricitabine, a 200 mg capsule (final dosage for marketing) and a 100 mg capsule (clinical trial dosage form) and to determine the effect of a high-fat meal on the bioavailability of emtricitabine administered as a 200 mg capsule. Each subject received three single doses of 200 mg emtricitabine treatments in a randomized fashion with balanced sequences: two 100 mg emtricitabine capsules, administered under fasting conditions (Treatment A); one 200 mg emtricitabine capsule administered under fasting conditions (Treatment B), and one 200 mg emtricitabine capsule, administered with a high-fat meal (Treatment C).

The 200 mg emtricitabine capsule formulation (final dosage for marketing) was bioequivalent to 100 mg emtricitabine capsule formulation which was used in pivotal clinical trials. The high-fat meal caused a decrease in mean C_{max} by approximately 29% and an increase in mean t_{max} by approximately 1.5 hrs, but had no effect on the extent (AUC_T, AUC_I) of systemic bioavailability of the 200 mg emtricitabine capsule formulation. The comparative bioavailability data are presented in Tables 9 and 10 below.

Table 9 Comparative Bioavailability Data – Study FTC–111

Emtricitabine (200 mg) From Measured Data Uncorrected for Potency				
Geometric Mean				
Arithmetic Mean (CV %)				
Parameter	Test¹ 1 x 200 mg Emtricitabine Capsule (Fasted)	Reference² 2 x 100 mg Emtricitabine Capsule (Fasted)	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (µg•hr/mL)	9.11 9.32 (22%)	8.92 9.12 (22%)	102.1	98.0–106.4
AUC _I (µg•hr/mL)	9.46 9.66 (21%)	9.31 9.50 (21%)	101.7	97.9–105.6
C _{max} (µg/mL)	1.95 2.01 (26%)	1.82 1.89 (29%)	107.3	99.9–115.3
T _{max} ³ (h)	NA ⁵ 1.00 (0.75, 1.51)	NA ⁵ 1.26 (0.75, 2.0)		
T _{1/2} ⁴ (h)	NA ⁵ 5.89 (18%)	NA ⁵ 6.17 (15%)		

1. Abbott Pharmaceuticals; North Chicago, IL, USA; Lot TP-0006-00205
2. Mallinckrodt-Hobart; Hobart, NY, USA; Lot TP-0006-00120
3. Expressed as the median (range).
4. Expressed as the arithmetic mean (CV%).
5. NA = Not Applicable

Table 10 Comparative Bioavailability Data – Study FTC–111

Emtricitabine (200 mg) From Measured Data Uncorrected for Potency				
Geometric Mean				
Arithmetic Mean (CV %)				
Parameter	Test¹ 1 x 200 mg Emtricitabine Capsule (Fed)	Reference¹ 1 x 200 mg Emtricitabine Capsule (Fasted)	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (µg•hr/mL)	8.28 8.38 (16%)	9.11 9.32 (22%)	90.9	86.6–95.8
AUC _I (µg•hr/mL)	8.59 8.69 (15%)	9.46 9.66 (21%)	90.8	86.3–95.4
C _{max} (µg/mL)	1.40 1.42 (17%)	1.95 2.01 (26%)	72.0	66.7–77.8
T _{max} ² (h)	NA ⁴ 2.51 (1.51, 4.00)	NA ⁴ 1.00 (0.75, 1.51)		
T _{1/2} ³ (h)	NA ⁴ 5.54 (7%)	NA ⁴ 5.89 (18%)		

1. Abbott Pharmaceuticals; North Chicago, IL, USA; Lot TP-0006-00205
2. Expressed as the median (range).
3. Expressed as the arithmetic mean (CV%).
4. NA = Not Applicable

DETAILED PHARMACOLOGY

MICROBIOLOGY

Mechanism of Action

Emtricitabine, a synthetic nucleoside analog of cytosine, 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 α , β , ϵ and mitochondrial DNA polymerase γ .

Antiviral Activity In Vitro

The in vitro antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% inhibitory concentration (IC_{50}) value for emtricitabine was in the range of 0.0013 to 0.64 μ M (0.0003–0.158 μ g/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity in vitro against HIV-1 clades A, B, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 μ M) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μ M).

In Vitro Drug Resistance

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

In Vivo Drug Resistance

Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 38% of treatment-naïve patients who were genotyped showed the presence of the M184V/I mutation in the HIV reverse transcriptase gene which is known to confer resistance to emtricitabine.

Cross Resistance

Cross-resistance among certain nucleoside analogue reverse transcriptase inhibitors has been recognized. Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected in vivo by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations 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

mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

TOXICOLOGY

Carcinogenesis

In long-term oral carcinogenicity studies of emtricitabine, no drug-related increase in tumor incidence was 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).

Mutagenesis

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

Impairment of Fertility

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.

Pregnancy

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 studies in pregnant women. Because animal reproduction studies are not always predictive of human response, EMTRIVA 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.

REFERENCES

1. Benaboud, S., et al. 2011. Concentrations of Tenofovir and Emtricitabine in Breast Milk of HIV-1 Infected Women in Abidjan, Côte d'Ivoire, in the ANRS 12109 TEMAA Study, Step 2. *Antimicrob. Agents Chemother.* 55: 1315-1317.

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

PrEmtriva®

(Emtricitabine Capsules)

This leaflet is part III of a three-part “Product Monograph” published when EMTRIVA was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about EMTRIVA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- EMTRIVA is a type of medicine called an HIV (human immunodeficiency virus) nucleotide analog reverse transcriptase inhibitor (NRTI).
- EMTRIVA is always used in combination with other anti-HIV medicines to treat people with HIV infection.
- EMTRIVA is for adults age 18 and older. EMTRIVA has not been studied fully in children under age 18 or adults over age 65.

What it does:

- EMTRIVA helps to block HIV reverse transcriptase (enzyme) that is needed for HIV to multiply. EMTRIVA lowers the amount of HIV in the blood (viral load).
- EMTRIVA does not cure HIV infection or AIDS. The long-term effects of EMTRIVA are not known at this time. People taking EMTRIVA may still get opportunistic infections or other conditions that happen with HIV infection. Opportunistic infections are infections that develop because the immune system is weak.
- EMTRIVA may also help increase the number of T cells called CD4 cells which are important to your immune system.
- **EMTRIVA does not lower your chance of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood.** For your health and the health of others it is important to always practice safe sex by using a latex or polyurethane condom or other barrier to lower the chance of sexual

contact with semen, vaginal secretions, or blood. Never use or share dirty needles.

When it should not be used:

- Do not take EMTRIVA if you are allergic to EMTRIVA or any of its ingredients (**See: What the important nonmedicinal ingredients are**).

What the medicinal ingredient is:

Emtricitabine

What the important nonmedicinal ingredients are:

Croscopovidone, magnesium stearate, microcrystalline cellulose and povidone.

Capsule shell contains gelatin.

What dosage forms it comes in:

EMTRIVA is available as capsules. Each capsule contains 200 mg of emtricitabine and inactive ingredients. EMTRIVA capsules have a blue cap and white body, printed with “200 mg” in black on the cap and “GILEAD” and the corporate logo in black on the body.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Some people who have taken nucleoside analog medications like EMTRIVA have developed a serious condition called lactic acidosis (build up of acid in the blood) and a condition called hepatotoxicity (serious liver problems), with hepatomegaly (liver enlargement) and steatosis (fat in the liver). Fatal cases have been reported. Lactic acidosis is a medical emergency and must be treated in the hospital.

If you have hepatitis B virus infection (inflammation of the liver), you may have a “flare-up” of hepatitis B, in which the disease suddenly returns in a worse way than before if you stop taking EMTRIVA. Your doctor will monitor your condition for several months after stopping EMTRIVA if you have both HIV and HBV infection. EMTRIVA is not approved for the treatment of Hepatitis B Virus infection.

BEFORE you use EMTRIVA talk to your doctor or pharmacist if:

- ***You are pregnant or planning to become pregnant:*** Pregnant mothers should not take EMTRIVA unless specifically directed by the doctor. If you take EMTRIVA while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- ***Your are breastfeeding or planning to breastfeed:*** Do not breastfeed if you are taking EMTRIVA or have HIV. Emtricitabine passes to your baby in your breast milk. You should not breastfeed because of the risk of passing HIV to your baby. Talk to your doctor about the best way to feed your baby.
- ***You have other medical conditions:*** Let your doctor know if you have other medical conditions, especially hepatitis (inflammation of the liver), and kidney problems.
- ***You are taking other medicines:*** Some medicines can interact when taken together, including prescription and non-prescription medicines and dietary supplements.

Changes in your immune system (Immune Reconstitution Syndrome) can happen when you start taking HIV medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time, or you could develop an autoimmune disease in which your immune system reacts against your own body (e.g. Grave's disease (which affects the thyroid gland), Guillain-Barre syndrome (which affects the nervous system) or polymyositis (which affects the muscles) and it may develop at any time, sometimes months later after the start of HIV therapy). Sometimes symptoms can be severe, so if you develop high temperature (fever), joint or muscle pain, redness, rash, swelling or fatigue, or any new symptoms, contact your doctor right away.

INTERACTIONS WITH THIS MEDICATION

Let your doctor know if you are taking any other medications.

Do not take EMTRIVA with other medications containing emtricitabine such as TRUVADA[®], ATRIPLA[®], COMPLERA[®] or STRIBILD[®] or other medications containing lamivudine such as Combivir[®], 3TC[®], Heptovir[®], Kivexa[®] or Trizivir[®]. because these medicines contain the same or similar active ingredients

PROPER USE OF THIS MEDICATION

Stay under a doctor's care when taking EMTRIVA.

Do not change your treatment or stop treatment without first talking with your doctor.

Carefully follow the directions and dosing schedule prescribed by your doctor.

When your EMTRIVA supply starts to run low, see your doctor or pharmacist for a refill. 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 EMTRIVA and become harder to treat.

Only take medicine that has been prescribed specifically for you. Do not give EMTRIVA to others or take medicine prescribed for someone else.

Usual Adult Dose

- The usual adult dose of EMTRIVA is one 200 mg capsule orally (by mouth) once a day, in combination with other anti-HIV medicines.
- EMTRIVA may be taken with or without food.

Overdosage

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose

- If you miss a dose of EMTRIVA, take it as soon as possible and then take your next scheduled dose at its regular time.
- Do not double the next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of EMTRIVA are Headache, Diarrhea, Nausea, Rash, Vomiting, Sleeplessness and Cough. Other side effects include Skin discoloration.

Changes in body fat have been seen in patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ('buffalo hump'), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Effect: Lactic acidosis Symptoms <ul style="list-style-type: none"> • Feeling very weak or tired • Unusual muscle pain • Stomach pain with nausea and vomiting • Feeling cold especially in arms and legs • Feeling dizzy or lightheaded • Fast or irregular heartbeat 		<ul style="list-style-type: none"> ✓ ✓ ✓ ✓ ✓ ✓ 	
Very Rare	Effect: Hepatotoxicity (severe liver problems) with hepatomegaly (liver enlargement) and steatosis (fat in the liver) Symptoms <ul style="list-style-type: none"> • Jaundice (skin or the white part of eyes turn yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain 		<ul style="list-style-type: none"> ✓ ✓ ✓ ✓ ✓ ✓ 	
Very Rare	Effect: Flare-ups of hepatitis B virus infection following drug discontinuation Symptoms <ul style="list-style-type: none"> • Jaundice (skin or the white part of eyes turn yellow) • Urine turns dark • Bowel movements (stools) turn light in color • Loss of appetite for several days or longer • Feeling sick to your stomach (nausea) • Lower stomach pain 		<ul style="list-style-type: none"> ✓ ✓ ✓ ✓ ✓ ✓ 	

This is not a complete list of side effects. For any unexpected effects while taking EMTRIVA, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep EMTRIVA and all other medications out of reach of children.
- EMTRIVA should be stored at 15–30 °C.
- 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.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the Medeffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:

www.gilead.ca

or requested by contacting the sponsor, Gilead Sciences, Inc., at:

1-866-207-4267

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