NEW ZEALAND DATA SHEET

1 EMTRIVA® (emtricitabine) Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Emtricitabine 200 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

EMTRIVA is available as 200 mg hard capsules.

Each EMTRIVA capsule has a white opaque body with light blue opaque cap. Each capsule is printed with "200 mg" on the cap and "GILEAD" and [Gilead logo] on the body in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EMTRIVA is indicated for the treatment of HIV in combination with other antiretroviral agents in adults and paediatric patients 12 years of age and older, weighing more than 33 kg.

Evidence to support this claim is based on surrogate markers (plasma HIV RNA and CD4 count) in antiretroviral naïve individuals and in antiretroviral experienced individuals with virological suppression (see section 5.1 Pharmacodynamic properties, Clinical trials).

4.2 Dose and method of administration

The recommended dose of EMTRIVA is one 200 mg hard capsule, taken orally once daily.

EMTRIVA may be taken with or without food.

Special populations: Dosage adjustment

Children (12 to 17 years inclusive): The recommended dose of EMTRIVA for paediatrics weighing more than 33 kg is one 200 mg hard capsule, taken orally once daily.

Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal impairment: Emtricitabine is eliminated by renal excretion and exposure to emtricitabine was significantly increased in patients with renal impairment (see section 5.2

Pharmacokinetic Properties: Pharmacokinetics in Special Populations). Dosing interval adjustment is required in all patients with creatinine clearance < 50 ml/min, as detailed in Table 1 below.

The safety and efficacy 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 1. Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (CL_{cr}) (ml/min)			
	≥ 50	30-49	15-29	< 15 (including patients requiring haemodialysis)*
Recommended 200 mg Dosing Interval	Every 24 hours	Every 48 hours	Every 72 hours	Every 96 hours

* Assumes a 3h haemodialysis session three times a week.

No data are available on which to make a dosage recommendation in paediatric patients with renal impairment.

***Hepatic Impairment*:** Based upon minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for EMTRIVA in patients with hepatic impairment. No data are available on which to make a dose recommendation for patients with hepatic impairment.

4.3 Contraindications

EMTRIVA is contraindicated in patients with known hypersensitivity to emtricitabine or any other components of the capsule.

EMTRIVA should not be administered concomitantly with other products containing emtricitabine or products containing lamivudine.

4.4 Special warnings and precautions for use

General

Emtricitabine is not recommended for use in monotherapy for the treatment of HIV infection.

Patients receiving emtricitabine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Patients should be advised that antiretroviral therapies, including emtricitabine have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be used. Patients should also be informed that emtricitabine is not a cure for HIV infection.

When deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the patterns of mutations associated with different medicinal products and the treatment history of the individual patient. Where available, resistance testing may be appropriate. There is no experience of using emtricitabine in patients who are failing their current regimen or who have failed multiple regimens.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of antiretroviral nucleoside analogues alone or in combination, in the treatment of HIV infection. A majority of cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Patients at increased risk should be followed closely and dosing suspended in any patient who develops clinical/laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

All patients, with or without identifiable risk factors may develop this adverse event.

Renal Function

Emtricitabine is principally eliminated by the kidney via glomerular filtration and active tubular secretion. Co-administration of 200 mg emtricitabine with medicinal products that are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition of this elimination pathway. Reduction of dosage is recommended for patients with impaired renal function (see section 5.2 Pharmacokinetic properties and section 4.2 Dose and method of administration).

Lipodystrophy

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Liver function

Emtricitabine has not been evaluated in non-HBV infected patients with hepatic impairment. Patients with chronic hepatitis-B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events.

Post-treatment Exacerbation of Hepatitis

The safety and efficacy of emtricitabine in patients co-infected with HIV and HBV has not been fully established. Exacerbations of hepatitis B have been reported after discontinuation of emtricitabine treatment. These exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. In some of these patients, HBV reactivation was associated with more severe liver disease, including decompensation and liver failure.

Therefore, it is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus before initiating antiretroviral therapy. Co-infected patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with emtricitabine. There is insufficient evidence to determine whether re-initiation of emtricitabine alters the course of post-treatment exacerbations of hepatitis.

Immune Reconstitution Syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of antiretroviral therapy. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders 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.

Paediatric Use

The safety and efficacy of EMTRIVA in patients between 12 to 17 years of age is supported by data from three open-label, non-randomised clinical studies FTC-203, FTC-202 and FTC-211 (see section 5.1 Pharmacodynamic properties, Clinical trials).

Use in the Elderly

Clinical studies of EMTRIVA did not contain sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. 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 section 4.2 Dose and method of administration).

4.5 Interaction with other medicines and other forms of interaction

General

The potential for drug interactions with EMTRIVA has been studied in combination with indinavir, zidovudine, d4T, famciclovir and tenofovir disoproxil fumarate. There were no clinically significant drug interactions for any of these drugs (see section 5.2 Pharmacokinetic properties, Pharmacokinetic drug interactions).

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Emtricitabine did not affect fertility in female and male mice or in male rats at oral doses up to 1000 mg/kg/day and 3,000 mg/kg/day (52-77 and 132 times the clinical exposure based on AUC, respectively). No fertility effects were observed in the offspring of mice given up to 1,000 mg/kg/day oral emtricitabine (52 times the clinical exposure based on AUC) from gestation through lactation.

Teratology and reproductive toxicity

Emtricitabine showed no evidence of teratogenicity and did not adversely affect reproduction or embryofoetal development. A moderate reduction in weight gain was observed in pregnant rabbits at exposures ($AUC_{0\rightarrow24}$) that were at least 30-fold greater than the anticipated human exposure following the recommended dose of 200 mg once daily.

Use in Pregnancy

Pregnancy Category B1

Studies in mice and rabbits have shown that emtricitabine readily crosses the placenta.

No evidence of embryofoetal toxicity or teratogenicity was observed in pregnant mice or rabbits given oral doses of emtricitabine up to 1,000 mg/kg/day (52 and 130 times the clinical exposure based on AUC, respectively). Impaired weight gain observed in pregnant rabbits at doses >300 mg/kg/day was not associated with any adverse foetal effects (at least 33 times the clinical exposure based on AUC).

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.

Use in Lactation

No developmental toxicity was noted post-natally in the offspring of mice given oral emtricitabine up to 1,000 mg/kg/day (52 times the clinical exposure based on AUC) from gestation through lactation. Impaired weight gain observed in lactating mice at the 1,000 mg/kg/day dose was not associated with any adverse events on pup survival, developmental or reproductive parameters.

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 IC50 but 3 to 12 times lower than the Cmin achieved from oral administration of emtricitabine. 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 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive or use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with emtricitabine.

4.8 Undesirable effects

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 I-III 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) adult patients received EMTRIVA 200 mg (n=580) or comparator drug (n=431) for 48 weeks.

The most common adverse events that occurred in patients receiving EMTRIVA with other antiretroviral agents in clinical trials were headache, diarrhoea, 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, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the adverse reactions reported in adults, anaemia has been reported commonly and hyperpigmentation very commonly, in paediatric patients (study FTC-203).

A summary of EMTRIVA treatment emergent clinical adverse events in studies 301A and 303 is provided in Table 2.

Table 2. Selected Treatment-Emergent Adverse Events (All Grades, Regardless of Causality) Reported in ≥3% of EMTRIVA-Treated Patients in Either Study 301A or 303 (0-48 weeks)

	303		301A	
Adverse event	EMTRIVA + ZDV/d4T + NNRTI/PI (n=294)	Lamivudine + ZDV/d4T + NNRTI/PI (n=146)	EMTRIVA + didanosine + efavirenz (n=286)	d4T + 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				
Diarrhoea	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[1]	17%	14%	30%	33%

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

Laboratory Abnormalities

Very common (≥ 10%): creatine kinase elevation.
Common (≥ 1% and <10%): hypertriglyceridaemia, neutropaenia, elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), amylase elevation including pancreatic amylase elevation, hyperglycaemia, serum lipase elevation, hyperbilirubinaemia.

The adverse reaction profile in patients co-infected with HBV is similar to that seen in patients infected with HIV virus without co-infection with HBV, however, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

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 3 below.

Table 3. 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)	d4T + didanosine + efavirenz (n=285)
Percentage with Grade 3 or Grade 4 laboratory abnormality	31%	28%	34%	38%
ALT (>5.0 x ULN[1])	2%	1%	5%	6%
AST (>5.0 x ULN)	3%	<1%	6%	9%
Bilirubin (>2.5 x ULN)	1%	2%	<1%	<1%
Creatine kinase (>4.0 x ULN)	11%	14%	12%	11%
Neutrophils (<750 mm^3)	5%	3%	5%	7%
Serum amylase (>2.0 x ULN)	2%	2%	5%	10%
Serum glucose (<2.2 or >13.9 mmol/L)	3%	3%	2%	3%
Serum lipase (>2.0 x ULN)	<1%	<1%	1%	2%
Triglycerides (>8.47 mmol/L)	10%	8%	9%	6%

1. ULN=Upper limit of normal

Study 934 - Treatment Emergent Adverse Events

Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either EMTRIVA + VIREAD administered in combination with efavirenz (n=257) or Combivir (lamivudine/zidovudine) administered in combination with efavirenz (n=254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table 4).

Adverse events leading to study drug discontinuation occurred in significantly smaller number of patients in the TRUVADA (tenofovir DF/emtricitabine) group compared to the Combivir group (5% vs 11%, p=0.010). The most frequently occurring adverse event leading to study drug discontinuation was anaemia (including decreased haemoglobin), no patient in the TRUVADA group and 6% of patients in the Combivir group.

Table 4. Frequency of Adverse Reactions to EMTRIVA and/or VIREAD (Grade 2– 4) Occurring in ≥3% of Patients Receiving EMTRIVA and VIREAD (or TRUVADA) in Study 934 (0-144 weeks)[1]

	TRUVADA[2]+ EFV N=257	Combivir+EFV N=254
Gastrointestinal Disorders		
Diarrhoea	9%	5%
Nausea	9%	7%
Nervous System Disorders		
Headache	6%	5%
Dizziness	8%	7%
Psychiatric Disorders		
Insomnia	5%	7%
Abnormal Dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

1. Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.
2. Patients received EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.

Laboratory Abnormalities

Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 5).

Table 5. Grade 3/4 Laboratory Abnormalities Reported in >1% of Patients in Either Treatment Group, Study 934 (0–144 weeks)

	TRUVADA[1]+ EFV N=254	Combivir+EFV N=251
Any ≥ Grade 3 Laboratory Abnormality	30%	26%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	9%	7%
Serum Amylase (>175 U/L)	8%	4%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%
ALT (M: >215 U/L) (F: >170 U/L)	2%	3%
Hyperglycaemia (>250 mg/dL)	2%	1%
Haematuria (>75 RBC/HPF)	3%	2%
Neutrophil (<750/mm^3)	3%	5%
Triglyceride (>750 mg/dL)	5%	3%
Haemoglobin (<7.0 g/dL)	0%	2%

1. Patients received EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.

From Post Marketing Surveillance

Immune Reconstitution Syndrome: 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 section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions: https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For information on the management of overdose, contact the National Poisons Centre on 0800 764 766.

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.

Haemodialysis 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Emtricitabine belongs to the nucleoside and nucleotide reverse transcriptase inhibitors pharmacotherapeutic group (ATC Code: J05AF09).

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 μM. In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine (3TC), stavudine (d4T), 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 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μM).

When tested for activity against laboratory strains of HBV, the 50% inhibitory concentration (EC_{50}) value for emtricitabine was in the range of 0.01 to 0.04 μmol/l.

Clinical virology: HIV resistance to emtricitabine develops as the result of changes at codon 184 causing the methionine to be changed to a valine (an isoleucine intermediate has also been observed) of the HIV reverse transcriptase. This HIV mutation was observed *in vitro* and in HIV infected patients.

Genotypic resistance analysis was performed in Study 301A (see section 5.1 Pharmacodynamic properties, Clinical trials). This study was a double-blind, active-controlled multicentre study comparing emtricitabine administered in combination with didanosine and efavirenz versus

d4T, didanosine and efavirenz in 571 antiretroviral naïve adult patients. Genotypic resistance analysis was performed in 48 of the 50 patients with virological failure (greater than 400 copies/mL) identified during the course of the study (13 in the emtricitabine group and 35 of the 37 patients with failure in the d4T group). Virological failure with at least 1 new genotypic mutation developed in 12/286 (4%) patients in the emtricitabine group and 31/285 (11%) in the d4T group (P=0.005). Of these patients, 11 and 31 patients respectively developed an NNRTI-associated mutation. Five of the 11 emtricitabine group patients developed the M184/I mutation in addition to the NNRTI mutation and 1 developed a mutation at position K65N (possibly associated with didanosine).

Cross Resistance: Cross-resistance among certain nucleoside analog reverse transcriptase inhibitors has been recognised (see section 4.4 Special warnings and precautions for use). Emtricitabine resistant viruses with the M184V mutation are cross resistant with lamivudine and zalcitabine. Viruses with the K65R mutation selected for *in vivo* by use of abacavir, didanosine, tenofovir and zalcitabine demonstrate reduced susceptibility to inhibition by emtricitabine. Viruses which harbour mutations which confer reduced susceptibility to other NRTIs i.e. d4T and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) or the NNRTI group (K103N), remained sensitive to emtricitabine.

When deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the patterns of mutations associated with different medicinal products and the treatment history of the individual patient. Where available, resistance testing may be appropriate.

Clinical Trials

Adult Patients

Study 301A: EMTRIVA once daily + didanosine once daily + efavirenz once daily compared to d4T BID + didanosine once daily + efavirenz once daily

Study 301A was a 48 week double-blind, active-controlled multicentre study comparing EMTRIVA (200 mg once daily) administered in combination with didanosine and efavirenz versus d4T, didanosine and efavirenz in 571 antiretroviral naïve adult patients. Patients had a mean age of 36 years (range 18 to 69), 85% were male, 52% Caucasian, 16% African-American and 26% Hispanic. Patients had a mean baseline CD4 cell count of 318 cells/mm^3 (range 5-1317) and a median baseline plasma HIV RNA of 4.9 log_{10} 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 6 below.

Table 6. Outcomes of Randomised Treatment at Week 48 (Study 301A)

Outcome at Week 48	EMTRIVA+ didanosine+ efavirenz (N=286)	d4T+ didanosine+ efavirenz (N=285)	Difference (%) between groups (95% CI)
Responder (<400 copies/mL)[1]	81%	68%	13 (7, 20)
Responder (<50 copies/mL)[2]	78%	59%	19 (12, 27)
Virologic Failure[3]	3%	11%	-5 (-9, -2)
Death	0%	<1%	NA
Study Discontinuation Due to Adverse Event	7%	13%	-5 (-9, -0.3)
Study Discontinuation For Other Reasons[4]	9%	8%	2 (-2, 6)

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.
2. Patients achieved and maintained confirmed HIV RNA <50 copies/mL through Week 48.
3. Includes patients who failed to achieve virologic suppression (<400 copies/mL) or rebounded after achieving virologic suppression.
4. 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/mm^3 for the EMTRIVA arm and 134 cells/mm^3 for the d4T 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 d4T group.

Study 303: EMTRIVA once daily + Stable Background Therapy (SBT) compared to lamivudine BID + SBT

Study 303 was a 48 week, open-label, active-controlled multicentre study comparing EMTRIVA (200 mg once daily) to lamivudine, in combination with d4T or zidovudine and a protease inhibitor or NNRTI in 440 adult 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 randomised 1:2 to continue therapy with lamivudine (150 mg BID) or to switch to EMTRIVA (200 mg once daily). 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/mm^3 (range 37-1909), and a median baseline plasma HIV RNA of 1.7 $\log_{10}$ copies/mL (range 1.7-4.0).

The median duration of prior antiretroviral therapy was 27.6 months.

Table 7. Outcomes of Randomised Treatment at Week 48 (Study 303)

Outcome at Week 48	EMTRIVA + ZDV/d4T + NNRTI/PI (N=294)	Lamivudine + ZDV/d4T + NNRTI/PI (N=146)	Difference (%) between groups (95% CI)
Responder (<400 copies/mL)[1]	77%	82%	-3 (-10, 5)
Responder (<50 copies/mL)[2]	67%	72%	-3 (-11, 6)
Virologic Failure[3]	7%	8%	-1, (-4, 3)
Death	0%	<1%	NA
Study Discontinuation Due to Adverse Event	4%	0%	4 (2, 7)
Study Discontinuation For Other Reasons[4]	12%	10%	2 (-3, 8)

1. Patients achieved and maintained confirmed HIV RNA <400 copies/mL through Week 48.

2. Patients achieved and maintained confirmed HIV RNA <50 copies/mL through Week 48.

3. Includes patients who failed to achieve virologic suppression (<400 copies/mL) or rebounded after achieving virologic suppression.

4. 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/mm^3 for the EMTRIVA arm and 61 cells/mm^3 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.

Study 934: EMTRIVA + VIREAD + efavirenz compared with combivir (lamivudine/zidovudine) + efavirenz

Study 934 is a randomised, open-label, active controlled multicentre study comparing two different dosing regimens in 511 antiretroviral-naïve HIV-1 infected adult patients. Patients were randomised to receive either EMTRIVA + VIREAD administered in combination with efavirenz or Combivir (lamivudine/zidovudine) administered in combination with efavirenz. For patients randomised to receive EMTRIVA + VIREAD the two drugs were administered individually for the first 96 weeks and then switched to TRUVADA (fixed dose combination of tenofovir DF 300 mg/emtricitabine 200 mg) during weeks 96 to 144, without regard to food.

For inclusion in the study, antiretroviral treatment naïve adult patients (≥ 18 years) with plasma HIV RNA greater than 10,000 copies/mL, must have an estimated glomerular filtration rate as measured by Cockroft-Gault method of ≥ 50 mL/min, adequate haematologic function, hepatic transaminases and alanine aminotransferases ≤ 3 ULN, total bilirubin ≤ 1.5 mg/dL, serum amylase ≤ 1.5 ULN and serum phosphorus ≥ 2.2 mg/dL. Exclusion criteria included: a new AIDS defining condition diagnosed within 30 days (except on the basis of CD4 criteria),

ongoing therapy with nephrotoxic drugs or agents that interacted with efavirenz, pregnancy/lactation, a history of clinically significant renal / bone disease or malignant disease other than Kaposi's sarcoma or basal-cell carcinoma, or a life expectancy of less than one year. If efavirenz-associated central nervous system toxicities occurred, nevirapine could be substituted for efavirenz. Patients who were not receiving their originally assigned treatment regimen after week 48 or 96 and during the 30-day extension study window were not eligible to continue to weeks 96 or 144 respectively.

Patients 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^3 (range 2 to 1191) and median baseline plasma HIV-1 RNA was 5.01 log_{10} copies/mL (range 3.56 to 6.54). Patients were stratified by baseline CD4 count (< or ≥ 200 cells/mm^3); 41% had CD4 cell counts <200 cells/mm^3 and 51% of patients had baseline viral loads >100,000 copies/mL Treatment outcomes at 48 and 144 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 8.

Table 8. Outcomes of Randomised Treatment at Weeks 48 and 144 (Study 934) in Treatment Naïve Patients

	WEEK 48		WEEK 144	
Outcome at Weeks 48 and 144	EMTRIVA + VIREAD + EFV (N=244)	Combivir + EFV (N=243)	TRUVADA[4] + EFV (N=227)	Combivir + EFV (N=229)
Responder[1]	84%	73%	71%	58%
Virologic failure[2]	2%	4%	3%	6%
Rebound	1%	3%	2%	5%
Never suppressed	0%	0%	0%	0%
Change in antiretroviral regimen	1%	1%	1%	1%
Death[3]	<1%	1%	1%	1%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL.
3. All deaths were unrelated to study drugs.
4. Patients received EMTRIVA + VIREAD up to week 96 and switched to TRUVADA from week 96 to 144.

In this study, EMTRIVA + VIREAD in combination with efavirenz was statistically significantly superior to Combivir in combination with efavirenz with regards to the primary and secondary endpoints: achieving and maintaining HIV-1 RNA <400 copies/mL through 48 and 144 weeks (Table 6). The difference in the proportions of responders between the EMTRIVA + VIREAD group and the Combivir group was 11.4%, and the 95% CI was 4.3% to 18.6% (p=0.002) at week 48 and a difference of 12.9% (95% CI was 4.2% to 21.6%, p=0.004) at week 144.

Through 48 weeks of therapy, 80% and 70% of patients in the EMTRIVA + VIREAD and the Combivir arms, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The difference in the proportions of responders between the EMTRIVA + VIREAD group and the Combivir group was 9.1%, and the 95% CI was 1.6% to 16.6% (p=0.021) at week 48. The proportion of patients responding at 144 weeks of therapy was higher in the TRUVADA group (64%) compared with the Combivir group (56%); p=0.082, a difference of 8.1% and the 95% CI was -0.8% to 17.0%.

The mean increase from baseline in CD4 cell count was 190 cells/mm^3 and 312 cells/mm^3 for the EMTRIVA + VIREAD + efavirenz arm, and 158 cells/mm^3 and 271 cells/mm^3 for the Combivir + efavirenz arm (p=0.002 and p=0.088) at weeks 48 and 144 respectively.

Resistance analysis was performed on HIV isolates from all patients with > 400 copies/mL of HIV-1 RNA at week 144 while on study drug or after treatment switch. Genotypic resistance to efavirenz, predominantly the K103N mutation, was the most common form of resistance that developed in both treatment arms. Resistance to efavirenz occurred in 68% (13/19) analysed patients in the TRUVADA group and in 72% (21/29) analysed patients in the Combivir group. The M184V mutation, associated with resistance to emtricitabine and lamivudine developed significantly less in the analysed patients in the TRUVADA group 11% (2/19) compared with the analysed patients in the Combivir group, 34% (10/29). Two patients in the Combivir group developed thymidine analog mutations, specifically D67N or K70R mutations in the reverse transcriptase gene.

Paediatric Patients

Studies FTC-202, FTC-203 and FTC-211

In three open-label, non-randomized clinical studies (Studies FTC-202, FTC-203, and FTC-211), EMTRIVA was administered to 169 HIV-1 infected treatment-naïve and experienced (defined as virologically suppressed on a lamivudine containing regimen for which EMTRIVA was substituted for lamivudine) patients in the following age groups: 3 to 24 months, 25 months to 6 years (FTC-203 only), 7 to 12 years, 13 to 17 years and 18 to 21 years.

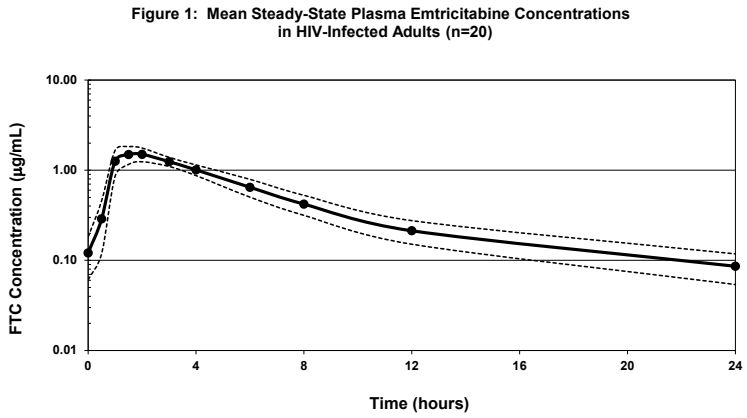
Through 48 weeks of therapy, the overall proportion of patients who achieved and sustained an HIV-1 RNA < 400 copies/mL was 86%, and < 50 copies/mL was 73%. The mean increase from baseline in CD4 cell count was 232 cells/mm^3 (−945, +1512).

5.2 Pharmacokinetic properties

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 (± 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. In 20 HIV infected subjects receiving 200 mg emtricitabine daily, steady-state plasma emtricitabine peak concentrations (C_{max}), trough concentrations (C_{min}) and area under the plasma concentration time curve over a 24-hour dosing interval (AUC) were 1.8±0.7 µg/ml, 0.09±0.7 µg/ml and 10.0±3.1 h.µg/ml, respectively. The mean steady-state plasma trough concentration at 24 hours post-dose was equal to or greater than the mean *in vitro* IC_{90} value for anti-HIV activity (IC_{90} 0.09 µg/ml).

The absolute bioavailability of EMTRIVA 200 mg capsules was estimated to be 93%.

Effects of Food on Oral Absorption

Administration of emtricitabine 200 mg hard capsules with a high-fat meal did not affect systemic exposure ($AUC_{0-\infty}$) whilst C_{max} decreased by 29%. Therefore EMTRIVA 200 mg hard capsules may be administered with or without food.

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. Distribution of emtricitabine to central nervous system has not been studied.

The apparent volume of distribution after intravenous administration of emtricitabine was 1.4±0.3 l/kg, indicating that emtricitabine is widely distributed throughout the body to both intracellular and extracellular fluid spaces.

Metabolism

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following oral administration of ^{14}C-emtricitabine, complete recovery of the dose was achieved in urine (~ 86%) and faeces (~ 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.

Excretion

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (~ 86%) and faeces (~ 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 ml/min (4.03 ml/min/kg). Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours. The renal clearance of emtricitabine is greater than the estimated creatinine clearance, which suggests elimination by both glomerular filtration and active tubular secretion.

Linearity/non-linearity

The pharmacokinetics of emtricitabine are proportional to dose over a dose range of 25 to 200 mg following single or repeated administration.

Special Populations

Age, Gender, and Ethnicity: In general, emtricitabine pharmacokinetics in children (aged 12 to 18 years of age) are similar to those seen in adults.The pharmacokinetics of emtricitabine have not been fully evaluated in the elderly. No clinically important differences have been identified due to gender or ethnicity.

Renal impairment: The pharmacokinetics of emtricitabine are altered in patients with renal impairment (see section 4.4 Special warnings and precautions for use). In patients with creatinine clearance < 50 ml/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, AUC of emtricitabine were increased due to a reduction in renal clearance (Table 9). It is required 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 section 4.2 Dose and method of administration).

Table 9. Mean ± SD Pharmacokinetic Parameters in Patients with Varying Degrees of Renal Function

Creatinine clearance (mL/min)[1]	>80 (n=6)	50-80 (n=6)	30-49 (n=6)	<30 (n=5)	ESRD* <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 (hr●μg/mL)	11.8 ± 2.9	19.9 ± 1.1	25.0 ± 5.7	34.0 ± 2.1	53.2 ± 9.9
CL/F (mL/min)	302 ± 94	168 ± 10	138 ± 28	99 ± 6	64 ± 12
CLr (mL/min)	213.3 ± 89.0	121.4 ± 39.0	68.6 ± 32.1	29.5 ± 11.4	-

*ESRD patients requiring dialysis; "-" = not applicable
1 Creatinine clearance calculated using the Cockcroft Gault equation

In patients with ESRD requiring haemodialysis approximately 30% of the emtricitabine dose was recovered in dialysate over a 3-hour dialysis period started within 1.5 hours of emtricitabine dosing (blood flow rate of 400 ml/min and a dialysate flow rate of ~ 600 ml/min).

Hepatic impairment: Pharmacokinetics of emtricitabine have not been fully elucidated in persons with hepatic impairment.

Pharmacokinetic/Pharmacodynamic relationship: 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 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.

Intracellular pharmacokinetics: In a clinical study the intracellular half-life of emtricitabine-triphosphate in peripheral blood mononuclear cells (PBMCs) was 39 hours and intracellular triphosphate levels increased with dose, but reached a plateau at doses of 200 mg or greater.

Pharmacokinetic 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 CYP450 isoforms: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, and 3A4. Emtricitabine did not inhibit uridine-5-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation. 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.

EMTRIVA has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (DF), indinavir, famciclovir, zidovudine, and d4T. Tables 10 and 11 summarise the pharmacokinetic effects of co-administered drug on emtricitabine pharmacokinetics and effects of emtricitabine on the pharmacokinetics of co-administered drug.

Table 10. Drug Interactions: Change in Pharmacokinetic Parameters for Emtricitabine in the Presence of the Co-administered Drug[1]

Co-administered Drug	Dose of Co-Administered 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)
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-
d4T	40 x 1	200 x 1	6	⇔	⇔	-
Zidovudine	300 BID x 7 days	200 once daily x 7 days	27	⇔	⇔	⇔

1 All interaction studies conducted in healthy volunteers

2 ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

Table 11. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Emtricitabine[1]

Co-administered Drug	Dose of Co-Administered Drug (mg)	Emtricitabine Dose (mg)	N	% Change of Co-administered 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	⇔	⇔	⇔
Indinavir	800 x 1	200 x 1	12	⇔	⇔	-
Famciclovir	500 x 1	200 x 1	12	⇔	⇔	-
d4T	40 x 1	200 x 1	6	⇔	⇔	-
Zidovudine	300 BID x 7 days	200 once daily x 7 days	27	↑ 17 (0 to ↑ 38)	↑ 13 (↑ 5 to ↑ 20)	⇔

1 All interaction studies conducted in healthy volunteers

2 ↑ = Increase; ↓ = Decrease; ⇔ = no effect; "-" = not applicable

There are no clinically significant interactions when emtricitabine is co-administered with either: indinavir, zidovudine, d4T, famciclovir, or tenofovir disoproxil fumarate.
There is no clinical experience of co-administration of emtricitabine with other cytidine analogues. Use of emtricitabine in combination with lamivudine or zalcitabine is not recommended.

Emtricitabine is primarily excreted renally via glomerular filtration and active tubular secretion. Apart from famciclovir and tenofovir disoproxil fumarate, the effect of co-administration of 200 mg emtricitabine with medicinal products that are excreted renally, or other medicinal products known to affect renal function has not been evaluated. Co-administration of 200 mg emtricitabine with medicinal products that are eliminated by active tubular secretion may lead to an increase in serum concentrations of either emtricitabine or a co-administered medicinal product due to competition for this elimination pathway.

5.3 Preclinical safety data

Cytotoxicity

There was no evidence of toxicity to mitochondria *in vitro*.

Carcinogenicity

There was no evidence of tumourigenesis in mice or rats given emtricitabine for 2 years at oral doses up to 750 mg/kg/day and 600 mg/kg/day, (30-33 and 34-42 times the clinical exposure based on AUC, respectively).

Genotoxicity

Emtricitabine is not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo.*

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EMTRIVA hard capsules contain the following ingredients as excipients: microcrystalline cellulose (E460), crospovidone, magnesium stearate (E572), povidone, purified water.

Capsule shell: gelatin, indigo carmine (CI 73015) (E132), titanium dioxide (E171).

Printing ink: iron oxide black (CI77499) (E172) and shellac (E904).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

EMTRIVA should be stored below 30 °C.

6.5 Nature and contents of container

Hard capsules are packaged in white high density polyethylene (HDPE) bottles containing 30 capsules.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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