CLINICAL UPDATE

Brand Name	Truvada®
Generic Name	emtricitabine-tenofovir disoproxil fumarate
Drug Manufacturer	Amneal Pharmaceuticals LLC

Clinical Update

TYPE OF CLINICAL UPDATE

New Generic Strengths (100-150 mg, 133-200 mg, 167-250 mg)

FDA APPROVAL DATE

August 22, 2018

LAUNCH DATE

January 20, 2021

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Abbreviated New Drug Application (ANDA): 209721

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Two-drug combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), both HIV-1 nucleoside analog reverse transcriptase inhibitors, is indicated:

- in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg.
- HIV-1 PrEP: in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Individuals must have a negative HIV-1 test immediately prior to initiating for HIV-1 PrEP.

MECHANISMS OF ACTION

Emtricitabine: FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate (FTC-TP), which inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. FTC-TP is a weak inhibitor of mammalian DNA polymerases α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir Disoproxil Fumarate: TDF is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. TDF requires initial diester hydrolysis for conversion to tenofovir and subsequent

phosphorylations by cellular enzymes to form tenofovir diphosphate (TFV-DP), which inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. TFV-DP is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 200 mg/300 mg, 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg of emtricitabine and tenofovir disoproxil fumarate, respectively.

DOSE & ADMINISTRATION

Testing: Prior to or when initiating emtricitabine and tenofovir disoproxil fumarate tablets, test for hepatitis B virus infection. Prior to initiation and during use of emtricitabine and tenofovir disoproxil fumarate tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all individuals. In individuals with chronic kidney disease, also assess serum phosphorus.

HIV-1 Screening: Screen all individuals for HIV-1 infection immediately prior to initiating emtricitabine and tenofovir disoproxil fumarate tablets for HIV-1 PrEP and at least once every 3 months while taking emtricitabine and tenofovir disoproxil fumarate tablets, and upon diagnosis of any other sexually transmitted infections (STIs).

Treatment of HIV-1 Infection:

- Recommended dosage in adults and pediatric patients weighing at least 35 kg: One emtricitabine and tenofovir disoproxil fumarate tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food.
- Recommended dosage in pediatric patients weighing at least 17 kg: One emtricitabine and tenofovir disoproxil fumarate low-strength tablet (100 mg/150 mg, 133 mg/ 200 mg, or 167 mg/250 mg based on body weight) once daily taken orally with or without food.
- Recommended dosage in renally impaired HIV-1 infected adult patients:
    - Creatinine clearance (CrCl) 30–49 mL/min: 1 tablet every 48 hours.
    - CrCl below 30 mL/min or hemodialysis: emtricitabine and tenofovir disoproxil fumarate tablets are not recommended.

HIV-1 Pre-Exposure Prophylaxis (PrEP):

- Recommended dosage in HIV-1 uninfected adults and adolescents weighing at least 35 kg: One emtricitabine and tenofovir disoproxil fumarate tablet (containing 200 mg of FTC and 300 mg of TDF) once daily taken orally with or without food.
- Recommended dosage in renally impaired HIV-uninfected individuals: emtricitabine and tenofovir disoproxil fumarate tablets are not recommended in HIV-uninfected individuals if CrCl is below 60 mL/min.

EFFICACY

The efficacy and safety of emtricitabine and tenofovir disoproxil fumarate have been evaluated in the studies summarized in below table.

Table 1: Trials Conducted with Emtricitabine and Tenofovir Disoproxil Fumarate for HIV-1 Treatment and HIV-1 PrEP

Trial	Population	Study Arms (N)[a]	Timepoint
Study 934[b] (NCT00112047)	HIV-infected, treatment-naïve adults	FTC+TDF + efavirenz (257) zidovudine/lamivudine + efavirenz (254)	48 Weeks
iPrEx[c] (NCT00458393)	HIV-seronegative men or transgender women who have sex with men	TRUVADA (1,251) Placebo (1,248)	4,237 person-years
Partners PrEP[c] (NCT00557245)	HIV serodiscordant heterosexual couples	TRUVADA (1,583) Placebo (1,586)	7,827 person-years

a. Randomized and dosed.
b. Randomized, open label, active-controlled trial.
c. Randomized, double-blind, placebo-controlled trial.

Study 934: Virologic Outcomes of Randomized Treatment at Weeks 48 and 144 (Study 934)

A randomized, open-label, active-controlled multicenter trial comparing FTC+TDF administered in combination with efavirenz (EFV) versus zidovudine (AZT)/lamivudine (3TC) fixed-dose combination administered in combination with EFV in 511 antiretroviral-naïve adult subjects.

Table 2 – Study 934 Results:

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

a. Subjects who were responders at Week 48 or Week 96 (HIV-1 RNA <400 copies/mL) but did not consent to continue trial after Week 48 or Week 96 were excluded from analysis.
b. Subjects achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Weeks 48 and 144.
c. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Weeks 48 and 144.
d. Includes lost to follow-up, subject withdrawal, noncompliance, protocol violation, and other reasons.

iPrEx Study/Results:

A randomized, double-blind, placebo-controlled multinational study in 2,499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behavior for HIV-1 infection. Subjects were followed for 4,237 person-years. The primary outcome measure was the incidence of documented HIV seroconversion. At the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the Truvada® group and 83 occurred in the placebo group, indicating a 42% (95% CI: 18–60%) reduction in risk. Risk reduction was found to be higher (53%; 95% CI: 34–72%) among subjects who reported previous unprotected anal intercourse (URAI) at screening (732 and 753 subjects reported URAI within the last 12 weeks at screening in the Truvada® and placebo groups, respectively). In a post-hoc case control study of plasma

and intracellular drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable intracellular tenofovir diphosphate concentrations. Efficacy was therefore strongly correlated with adherence.

Partners PrEP Study/Results:

A randomized, double-blind, placebo-controlled 3-arm trial conducted in 4,758 HIV-1 serodiscordant heterosexual couples in Kenya and Uganda to evaluate the efficacy and safety of TDF (N=1,589) and FTC/TDF (N=1,583) versus (parallel comparison) placebo (N=1,586) in preventing HIV-1 acquisition by the uninfected partner. Following 7,827 person-years of follow-up, 82 emergent HIV-1 seroconversions were reported, with an overall observed seroincidence rate of 1.05 per 100 person-years. Of the 82 seroconversions, 13 and 52 occurred in partner subjects randomized to Truvada® and placebo, respectively. Two of the 13 seroconversions in the Truvada® arm and 3 of the 52 seroconversions in the placebo arm occurred in women during treatment interruptions for pregnancy. The risk reduction for Truvada® relative to placebo was 75% (95% CI: 55–87%). In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable plasma tenofovir concentrations. Efficacy was therefore strongly correlated with adherence.