Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016

Application for Inclusion of Emtricitabine and Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablets (Truvada®) as pre-exposure prophylaxis (PrEP) on the WHO Model List of Essential Medicines (WHO EML)

Submitted by

Gilead Sciences Inc.

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Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016

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1. Summary statement of the proposal for inclusion

Emtricitabine (FTC) and tenofovir disoproxil fumarate (tenofovir DF, TDF) as the fixed dose combination tablet Truvada® (FTC/TDF) is already listed in the WHO EML as a treatment for HIV-1 infection in adults and children aged 12 years and older when used in combination with other antiretroviral agents. Truvada® in combination with efavirenz is also listed in the updated consolidated WHO treatment guidelines as preferred first-line treatment of adults and adolescents with HIV-1 infection [WHO, 2016].

Truvada® is now proposed for the additional indication of oral pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. This indication is based on two randomized controlled trials (RCTs) that included men who have sex with men (MSM) and heterosexual serodiscordant couples at high risk of sexually acquiring HIV-1 infection.

The principal reasons for requesting this inclusion are as follows:

- Rates of HIV-1 infection are decreasing too slowly and in some populations, are still rising [WHO, 2015]
- Clinical trial results confirm the efficacy of the ARV drug combination emtricitabine/tenofovir for use as PrEP to prevent people from acquiring HIV in a wide variety of settings and populations. As a result, WHO has updated its recommendations and guidance for oral PrEP (containing TDF) to be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches [WHO, 2016]
- ART-based interventions that focus on Truvada® as oral PrEP are integral to the WHO’s comprehensive HIV prevention strategy that also includes condom use, voluntary medical male circumcision and needle and syringe exchange programmes for intravenous drug users (IDUs) [Baggaley et al, 2015]
- Additional prevention options (beyond condoms) are urgently required to address unmet needs in population groups that specifically include:
  - People who lack the negotiating skills or power to insist on condom use
  - Situations where condoms are not readily available
  - Serodiscordant couples for safer conception or where PrEP can act as a bridge until viral suppression is achieved in HIV-infected individuals on antiretroviral therapy (ART)
• Partners where there is no shared prevention decision-making.

- Evidence from trials suggests that Truvada for PrEP™ enables people to consider all their safer-sex strategies by addressing their fear and consequent denial of a higher risk of HIV [UNAIDS, 2015]

- When taken as prescribed, Truvada for PrEP™ can significantly reduce the risk of HIV-1 infection in high-risk individuals by over 90% [Grant RM et al, 2014]

- Truvada for PrEP™ has been extensively evaluated; a recent meta analysis of 18 trials revealed that the rate of adverse events was similar between PrEP and placebo groups. More cases of drug-resistant HIV infection were found among PrEP users who initiated PrEP while acutely HIV-infected, but incidence of acquiring drug-resistant HIV during PrEP use was low. Studies consistently found no association between PrEP use and changes in sexual risk behavior. PrEP was not associated with increased pregnancy-related adverse events or hormonal contraception effectiveness [Fonner VA et al, 2016].
2. Name of the focal point in WHO submitting or supporting the application

Gottfried Hirnschall, Director of the HIV/AIDS Department and the Global Hepatitis Programme (GHP) of the World Health Organization.

3. Name of the organization(s) consulted and/or supporting the application

World Health Organization

4. International Nonproprietary Name (INN, generic name) of the medicine

Truvada® is a single-tablet regimen that contains a fixed-dose combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF).

Emtricitabine (FTC, Emtriva®)
INN: Emtricitabine

Tenofovir disoproxil fumarate (TDF, Viread®)
Modified INN: Tenofovir disoproxil fumarate

5. Formulation proposed for inclusion

Each tablet of Truvada® contains 200 mg of FTC and 300 mg of TDF (which is equivalent to 245 mg of tenofovir disoproxil). The tablets are blue, capsule-shaped, film-coated, debossed with “GILEAD” on one side and with “701” on the other side. Truvada® for Access countries also contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil). The tablets are light blue, capsule-shaped, film-coated, debossed with “GILEAD” on one side. The qualitative composition of Truvada® tablets is as described in Table 1.
Table 1: Qualitative composition of Truvada® tablets.

<table>
<thead>
<tr>
<th>Tablet core</th>
<th>Film coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croscarmellose sodium</td>
<td>Glycerol triacetate (E1518)</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>Hyromellose (E464)</td>
</tr>
<tr>
<td>Magnesium stearate (E572)</td>
<td>Indigo carmine aluminum lake (E132)</td>
</tr>
<tr>
<td>Microcrystalline cellulose (E460)</td>
<td>Lactose monohydrate</td>
</tr>
<tr>
<td>Pregelatinized starch (gluten free)</td>
<td>Titanium dioxide (E171)</td>
</tr>
</tbody>
</table>

6. International availability

Truvada® is a registered trademark of Gilead Sciences, Inc, or its related companies in the USA and other countries.

Truvada® tablets are currently manufactured, packaged, labeled and tested for Gilead Sciences, Inc. at the facilities listed in Table 2. All of the sites are currently approved and listed in the US New Drug Application (NDA). The manufacturing steps conducted at all facilities are in compliance with European Union (EU) and US Food and Drug Administration (FDA) Good Manufacturing Practice (GMP) guidelines.

Gilead’s mission is to transform care for HIV and other life-threatening diseases. To achieve this, Gilead believes it is important to apply innovation not just to drug discovery but also to finding new ways to get affordable medicines to people in need as quickly as possible. Gilead’s model for HIV treatment provision in developing countries has evolved over time, in response to lessons learned, stakeholder feedback and evidence of program effectiveness. Gilead learned early on the importance of partnership and collaboration for increasing drug access. Today Gilead is committed to ensuring access to its products around the world and to this end, works with a network of regional business and generic licensing partners and other stakeholders to expand treatment globally.

To securely and efficiently distribute HIV medicines worldwide, Gilead began working in 2005 with a network of regional business partners. These include manufacturing partners in the
Bahamas and South Africa licensed by the US FDA and regional and local distribution partners covering Africa, Asia, the Caribbean, Eastern Europe, Latin America, the Middle East, and the Pacific region. Gilead has rapidly recognized the importance of generic licensing and under the terms of licensing agreements (available at www.gilead.com), partners are able to produce generic TDF-based HIV therapy for sale in 112 low- and middle-income countries. Partners set their own process and may also create fixed-dose combinations with other HIV medicines. Partners receive a full technology transfer of the Gilead manufacturing process, enabling them to quickly scale-up production.

**Table 2. Manufacturing, packaging, labeling and testing facilities for Truvada® tablets**

<table>
<thead>
<tr>
<th>Manufacturing Site</th>
<th>Function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patheon, Inc.</td>
<td>Manufacturing, packaging, labelling, release testing and stability testing</td>
</tr>
<tr>
<td>Toronto Regional Operations (TRO)</td>
<td></td>
</tr>
<tr>
<td>2100 Syntex Court</td>
<td></td>
</tr>
<tr>
<td>Mississauga, Ontario L5N 7K9 Canada</td>
<td></td>
</tr>
<tr>
<td>Patheon Inc.</td>
<td>Manufacturing, release testing</td>
</tr>
<tr>
<td>111 Consumers Drive</td>
<td></td>
</tr>
<tr>
<td>Whitby, Ontario L1N 5Z5 Canada</td>
<td></td>
</tr>
<tr>
<td>Takeda GmbH</td>
<td>Manufacturing, packaging, labelling, release testing</td>
</tr>
<tr>
<td>Lehnitzstrasse 70-98</td>
<td></td>
</tr>
<tr>
<td>Oranienburg, Brandenburg 16515 Germany</td>
<td></td>
</tr>
<tr>
<td>Gilead Sciences Limited UC</td>
<td>Manufacturing, packaging, labeling, release testing and drug product release</td>
</tr>
<tr>
<td>IDA Business and Technology Park</td>
<td></td>
</tr>
<tr>
<td>Carrigtoghill</td>
<td></td>
</tr>
<tr>
<td>County Cork</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td></td>
</tr>
<tr>
<td>Pharma GmbH</td>
<td>Manufacturing, release testing</td>
</tr>
<tr>
<td>Ostenfelder Strasse 51-61</td>
<td></td>
</tr>
<tr>
<td>Ennigerloh, 59320</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>Catalent Germany Schorndorf GmbH</td>
<td>Packaging, labelling</td>
</tr>
<tr>
<td>Steinbeisstrasse 2</td>
<td></td>
</tr>
<tr>
<td>Schorndorf, D-73614, Germany</td>
<td></td>
</tr>
<tr>
<td>Aspen Port Elizabeth (Pty) Ltd</td>
<td>Manufacturing, packaging, release testing and stability testing</td>
</tr>
<tr>
<td>Corner of Fairclough and Gibaud Roads</td>
<td></td>
</tr>
<tr>
<td>Korsten, Port Elizabeth 6020</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td></td>
</tr>
</tbody>
</table>
Currently, 16 Indian manufacturers and one South African company hold licenses to Gilead HIV medicines. Licensees have received more than 30 WHO pre-qualification and/or FDA tentative approvals for their products. Gilead has developed generic Indian licenses that provide significant capacity for supply of product in the least developed countries, and which now have a proven track record in delivering high volume/low margin and quality HIV products, and in achieving the lowest possible prices. In July 2011, Gilead amended its licensing agreements with Indian manufacturers to grant them future rights to produce generic versions of pipeline HIV medicines contingent upon regulatory approval. Also in July 2011, Gilead became the first innovator pharmaceutical company to sign an agreement with the Medicines Patent Pool (MPP), an international organization that expands access to medicines through the sharing of drug patents. Gilead has granted the MPP similar licensing terms to those of its Indian partners for Gilead HIV medicines, as well as future rights to generic single-tablet regimens (see www.medicinespatentpool.org for details). MPP may sub-license Indian manufacturers to produce these medicines for low- and middle-income countries. In its 2011 annual report MPP
said Gilead has set “new public health standards, beyond any previous voluntary licensing agreement with a pharmaceutical company” for transparency, scope, pipeline products, and flexibility [MPP, 2011].

7. Listing type requested

Listing is requested on the Model List of Essential Medicines as an example of the therapeutic class of HIV nucleoside/nucleotide analogue reverse transcriptase inhibitors.

8. Information supporting the public health relevance

8.1 Epidemiological information on disease burden

In the 30 years since HIV was first identified, more than 34 million people have died from AIDS-related causes, making HIV/AIDS one of the most devastating of all pandemics. Recent estimates suggest that worldwide there were an estimated 37 million people living with HIV infection, 1.1 million HIV-related deaths, and 2.1 million new HIV infections in 2015 [WHO 2016].

Moreover, WHO estimates that only 54% of people with HIV know their status. In the absence of universal testing and immediate access to ART, people will continue to become infected by partners who are unaware they have HIV, or if aware of their positive status are either unable or unwilling to take ART [WHO, 2016].

The UNAIDS Fast-Track approach, the 90–90–90 target, and the prevention target of reducing the number of people acquiring HIV by 75% by 2020, call for an expanded and accelerated scale-up of HIV treatment and combination prevention during the next 4 years. Using antiretroviral medicines for treatment and PrEP contributes synergistically to these targets and to the goal of zero discrimination [UNAIDS, 2014] [UNAIDS, 2015].

8.2 Assessment of current use

Across the world, some people are at much higher risk than others of acquiring HIV infection and are considered priority candidates for oral PrEP. They include MSM and people who inject drugs, as well as heterosexual men and women who engage in high-risk sexual behaviors or engage in sexual activity within a high prevalence area or social network [Truvada® USPI,
Factors that may place an individual at high risk include having a partner or multiple sex partners who are HIV-infected or of unknown HIV-1 status, being recently diagnosed with sexually transmitted infections, inconsistent or no condom use, engaging in transactional sex work, illicit use of drugs or alcohol dependence and being incarcerated [Jain et al, 2015].

Consistent with the risk-profile for acquisition of HIV infection, Truvada® is indicated in combination with safer sex practices for oral PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. This includes HIV-negative MSM and male-female sex partners when one partner has HIV-1 infection and the other does not.

Oral PrEP with Truvada® must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initial use and periodically during use. Since drug-resistant HIV-1 variants have been identified with the use of Truvada for PrEP™ following undetected acute HIV-1 infection, oral PrEP with Truvada® should not be initiated if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed. Once oral PrEP with Truvada® has been initiated, HIV-1 screening tests should be repeated every 3 months.

Because the effectiveness of oral PrEP with Truvada® depends on strict adherence to the recommended daily dosing schedule followed in clinical trials, all uninfected individuals should be counselled to keep rigidly to the schedule described below. In addition, uninfected individuals should be counselled about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections (STIs) that can facilitate HIV-1 transmission, such as syphilis and gonorrhea. Additional effort should be made to inform individuals about reducing sexual risk behavior and to support them in this endeavor [Truvada® USPI, 2016].

9. Treatment details

9.1 Indications and usage

Truvada® is indicated in combination with safer sex practices for oral PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. Truvada® should not be prescribed for oral PrEP in individuals with unknown or positive HIV-1 status. If clinical symptoms consistent with acute...
viral infection are present and recent (<1 month) exposures are suspected prior to initiating oral PrEP then PrEP should be delayed for at least one month and negative HIV-1 status reconfirmed [Truvada® USPI, 2016].

9.2 Dosage and administration

For oral PrEP, the recommended dose of Truvada® in HIV-1 uninfected adults is a single tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) taken once daily with or without food.

9.2.1 Special populations

Renal impairment: Truvada® should not be used in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using Truvada for PrEP™, potential causes should be evaluated and a re-assessment made of potential risks and benefits of continued use.

Chronic hepatitis B virus (HBV) infection: All individuals eligible for oral PrEP should be tested for the presence of chronic hepatitis B virus (CHB) before being given Truvada®. This is because although Truvada® is not an approved treatment for CHB, Viread, a component of Truvada®, is an approved CHB medication. As a result, severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued Truvada®. Therefore, hepatic function should be monitored closely in HBV-infected patients who discontinue Truvada®. If appropriate, initiation of anti-hepatitis B therapy may be warranted [Truvada® USPI, 2016].

9.3 Reference to existing WHO and other clinical guidelines

Evidence-based guidelines on oral PrEP were first issued by the WHO in 2012 [WHO, 2012] and were updated in 2015 and 2016 [WHO, 2016]. The Centers for Disease Control and Prevention (CDC) in the US has also issued guidance on PrEP for HIV infection, in which a single tablet of once-daily Truvada® is recommended for those considered at substantial risk of acquiring HIV infection (Table 3) [US Public Health Service, 2014].
### Table 3. Current CDC guidelines on clinical indications and treatment recommendations for oral PrEP for HIV infection [US Public Health Service, 2014]

<table>
<thead>
<tr>
<th>Detecting substantial risk of acquiring HIV infection:</th>
<th>Men Who Have Sex With Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sexual partner with HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recent bacterial STD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High number of sex partners</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• History of inconsistent or no condom use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Commercial sex work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sexual partner with HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Recent bacterial STD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High number of sex partners</td>
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</tr>
<tr>
<td>• History of inconsistent or no condom use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Commercial sex work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lives in high-prevalence area or network</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinically eligible:**
- Documented negative HIV test before prescribing PrEP
- No signs/symptoms of acute HIV infection
- Normal renal function, no contraindicated medications
- Documented hepatitis B virus infection and vaccination status

**Prescription**
- Daily, continuous, oral doses of TDF/FTC (Truvada®), ≤90-day supply

**Other services:**
- Follow-up visits at least every 3 months to provide
- HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STD symptom assessment
- At 3 months and every 6 months after, assess renal function
- Every 6 months test for bacterial STDs
- Do oral/rectal STD testing
- Assess pregnancy intent
- Pregnancy test every 3 months
- Access to clean needles/syringes and drug treatment services


Note: In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected. For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about use during pregnancy.

Consistent with FDA labeling for Truvada®, the CDC guidelines stress the importance of HIV testing before PrEP is prescribed and at 3-month intervals thereafter. Regular testing is designed to ensure that anyone on PrEP who becomes infected with HIV discontinues PrEP and switches to an HIV treatment regimen so as to minimize the risk of drug resistance.

Guidelines issued by the WHO and CDC are complemented by national guidelines from a number of countries, including the National Strategic Plan (NSP) for HIV, STIs and TB (2012-2016) in South Africa, where the Southern African HIV Clinicians Society published a revised and expanded set of PrEP guidelines in early 2016 advising PrEP as a highly effective and safe prevention option for HIV prevention when combined with other combination prevention strategies. In Kenya, Truvada for PrEP™ is also included in the Guidelines on use of ARV drugs for treating and preventing HIV infections in Kenya – 2016 edition.
10. Summary of comparative effectiveness in a variety of clinical settings

10.1 Identification of clinical evidence

Evidence for the effectiveness of Truvada® as oral PrEP in populations at high risk of acquiring HIV infection has been demonstrated in a series of large, multinational RCTs the results of which have been published in peer-reviewed journals. Overall, they provide evidence of the viability of oral PrEP in prevention of HIV infection in at-risk, uninfected individuals. Open-label extensions to these trials as well as a number of other planned or ongoing studies, the details of which have been described in a recent review [Wilton et al, 2015], address issues beyond the constraints of an RCT that include identifying barriers to wider uptake of oral PrEP.

10.2 Summary of available data on comparative effectiveness of Truvada®

The original US indication for Truvada for PrEP™ was based on two placebo-controlled studies, iPreX and Partners PrEP. In addition to oral PrEP or placebo, all study participants received comprehensive HIV prevention services, including risk reduction counseling, condoms, and STI screening/treatment. A majority of the individuals enrolled, were from sub-Saharan Africa, South America and Asia. In these two pivotal trials, overall efficacy was 42% and 75% reduction in HIV-1 acquisition, respectively. Efficacy was strongly related to adherence. In those patients with detectable drug level, adherence increased to ≥90%. Two placebo controlled, women-only studies reflected both low adherence and low efficacy.
Table 4. Summary of results of the six RCTs of Truvada® as oral PrEP

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Participants</th>
<th>Drug</th>
<th>mITT Efficacy % (95% CI)</th>
<th>Efficacy When TDF was Detected in the Blood % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrEx</td>
<td>HIV negative MSM</td>
<td>TVD</td>
<td>44 (15-63)</td>
<td>92 (40-99)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>HIV serodiscordant couples</td>
<td>TVD</td>
<td>75 (55-87)</td>
<td>90 (58-98)</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexual men and women</td>
<td>TVD</td>
<td>62 (22-83)</td>
<td>78&lt;sup&gt;a&lt;/sup&gt; (58-83)</td>
</tr>
<tr>
<td>VOICE</td>
<td>Heterosexual women</td>
<td>TVD</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>FEM PrEP</td>
<td>Heterosexual women</td>
<td>TVD</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PROUD</td>
<td>HIV negative MSM</td>
<td>TVD</td>
<td>86 (90% CI: 58-96)</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup> Efficacy is the prevention of seroconversion. TFV detection assays were done in subsets of persons randomly assigned to receive FTC/TDF.

<sup>b</sup> Analysis of seroconverters who converted within 30 days of last medication

NR - No reported efficacy    NS- Not Significant

10.3 Summary of the efficacy of Truvada® for oral PrEP

In an analysis of demonstration projects and “real world” analyses, PROUD and Kaiser, Truvada for PrEP™ efficacy overall was high in both women and men, compared with placebo-controlled trials. In the active treatment arms of clinical studies, seroconversion rates varied from 0.5 to 4.7 per 100 person-years of Truvada® exposure, with FemPrEP and VOICE trials driving the highest rates. However, HIV-1 seroconversion data from 32 demonstration projects with 8478 participants, was 0.95/100 person-years. In women, the seroconversion rate was 0.25/100 person years, much lower than the 4.7/100 person-years observed in VOICE and FEMPrEP [McCallister 2016].

In the “real world” analysis, PROUD, the efficacy of Truvada for PrEP™ was seen to be 86% compared with a delayed treatment arm [McCormack 2016]. Of 1045 referrals to the Kaiser Permanente, San Francisco Medical Center between 2012 and February 2015 (99% of which were MSM), 657 were prescribed oral Truvada for PrEP™. Over a 2.5-year period there were no seroconversions observed, although rates of STIs were high [Volk et al, 2015]. These findings suggest it is possible to achieve zero incidence of new infections with Truvada for PrEP™ in “real world” settings [Volk et al, 2015]. Evidence from trials suggests that PrEP can enable people to consider all their safer-sex strategies by addressing their fear and consequent denial of a higher risk of HIV [UNAIDS, 2016].
10.4 Summary of the resistance profile of Truvada® following oral PrEP

The potential for the development of viral mutations that are resistant to treatment with nucleos(t)ide analogs is an important consideration in people receiving oral antiviral agents for HIV infection and the same is true for HIV-uninfected individuals receiving Truvada for PrEP™. The evidence summary published by the National Institute for Health and Care Excellence (NICE) shows that the use of Truvada® for PrEP in RCTs was associated with very few cases of drug resistance among HIV uninfected individuals. In RCTs, drug resistance occurred when Truvada® was used alone in individuals unknowingly started on Truvada® with undiagnosed acute HIV infection [NICE, 2016]. This underpins the need to determine HIV status before initiating oral PrEP with Truvada® [Truvada® USPI, 2016].

Recently, the risk of drug resistance with Truvada® or TDF pre-exposure prophylaxis (PrEP) was examined across six RCTs and one demonstration project. Overall, the absolute risk of excess drug resistance during Truvada® was 0.05% (5/9222) with the number needed to harm (NNH) as 1844, whilst the number needed to prevent one HIV infection was 13–60 [Grant et al, 2016]. The analysis supports recent guidance on the use of PrEP from the New York State Department of Health AIDS Institute, which suggests that rapid third-generation antibody tests are sufficient to minimize the overall risk of drug resistance from PrEP [New York State Department of Health AIDS Institute, 2015].

10.5 Summary of available estimates of comparative effectiveness

Truvada® is currently the only antiretroviral agent approved by the FDA for use as oral PrEP in individuals considered at high risk of exposure to HIV. Clinical trials that formed the basis of FDA approval show that it confers significant protection in HIV uninfected individuals when taken as prescribed. Despite some initially disappointing results from two trials in vulnerable women living in sub-Saharan Africa, which were associated with very low adherence rates, results from other trials in low-income countries suggest that adherence with oral PrEP can reach up to or equal to 90%. Moreover, open-label studies which are more reflective of “real world” settings and where everyone eligible is offered Truvada® suggest that adherence is greater than that seen in the earlier placebo-controlled RCTs.
Taken as prescribed, Truvada® can reduce the risk of infection by more than 90% in at-risk individuals that include MSM, serodiscordant couples and heterosexuals. The trials also showed no evidence of risk compensation as measured by decreased condom use or increased number of sexual partners. As drug resistance is much more likely to occur if Truvada® is used alone in individuals unknowingly infected with HIV, Truvada® should not be started as oral PrEP in any individual showing signs or symptoms of acute viral infection unless their HIV status has been confirmed.

Because recipients of oral PrEP with Truvada® must first undergo testing for HIV infection status there is scope to identify undiagnosed HIV earlier as well as other STIs and provide treatment. Once started on oral PrEP, uninfected individuals will have access to regular HIV testing (at least every 3 months), monitoring for drug-related side effects and support to encourage long-term adherence to PrEP as well as guidance on risk-reduction measures. Thus, oral PrEP with Truvada® has potential to provide benefits that extend beyond its direct effect on HIV prevention. In the open-label extension to iPrEX, oral PrEP with Truvada® improved mental health in MSM by alleviating some of the anxiety, guilt and fear associated high-risk sexual behaviors and their association with increased risk of HIV [Koester et al, 2014].

11. Summary of comparative evidence on safety

11.1 Estimate of total patient exposure to Truvada®

Truvada® has been available as a treatment for HIV-1 infection for more than a decade during which time approximately 7.6 million people infected with HIV across the world have received tenofovir-based regimens. Following its approval for oral PrEP by the US FDA in 2012, exposure to Truvada® has increased steadily from a relatively low baseline. A Gilead-sponsored study of oral PrEP uptake in the US showed that there was a 332 increase of Truvada for PrEP™ usage when comparing the first 3 months of 2014 to the first 3 months in 2015 (from 529 individuals to 1761) [Bush et al 2015].

PrEP use in United States was also assessed using national, electronic, patient-level data collected from 80% of United States retail pharmacies that dispensed Truvada® between Jan 2012 and December 2015. An algorithm was used to distinguish between patients receiving
Truvada for PrEP™ and those receiving Truvada® for either HIV treatment, HIV post-exposure prophylaxis or chronic hepatitis B treatment. The study reported that 79,684 unique individuals started Truvada for PrEP™ with an increase from 1671 at end of 2012 to 14,000 in last quarter of 2015, a 738% increase. It was further reported that 75% of PrEP use was in men. In addition, 28% of women starting PrEP were <25 years of age compared to only 11% of men under 25 [Mera, 2016].

These numbers are in addition to the thousands of individuals receiving Truvada® as part of oral PrEP demonstration projects, open-label extensions to RCTs, Gilead medication assistance programs, as well as routine clinical practice at the Kaiser Permenante, San Francisco Medical Center, U.S.

In another recently published retrospective analysis of the 2010–2014 MarketScan database, a national sample of persons with commercial health insurance in the United States was analyzed for PrEP uptake. A significantly increasing trend in the proportion of persons prescribed Truvada® for PrEP over the study period, was observed with 417 users in 2010 and 9375 unique individuals in 2014 (P<0.001). In 2014, among PrEP users 97% were male and 98% resided in metropolitan areas [Wu et al, 2016].

### 11.2 Description of adverse effects/reactions

The NICE evidence summary shows that the use of Truvada® for PrEP was well tolerated by participants enrolled in RCTs [NICE, 2016]. None of the studies found any significant safety concerns with daily oral PrEP and no new adverse reactions to Truvada® were identified [Truvada® USPI, 2016]. Some trial participants reported adverse events that included nausea, gastrointestinal upset, fatigue, vomiting and dizziness but these were mild and usually resolved within the first month of taking Truvada®. Compared with placebo, small decreases in creatinine clearance were seen in individuals taking Truvada® in RCTs; however, the decreases stabilized within the first month, were not considered clinically meaningful and resolved once medication stopped [Solomon et al, 2014; Mugwanya et al, 2015].

### 11.3 Renal safety profile

Because tenofovir and emtricitabine are principally excreted via the kidney, the renal safety
profile of Truvada® has been studied in detail [Truvada® USPI, 2016]. Truvada® for oral PrEP in an HIV-1 uninfected individual should therefore not be used where estimated creatinine clearance is below 60 mL/min.

11.4 Impact of Truvada® on bone health

Studies in HIV infected people have shown TDF to be associated with small but significant decreases in bone mineral density (BMD) and the same effect was seen in HIV uninfected individuals enrolled in the oral PrEP trials [Kasonde et al, 2014; Mulligan et al, 2015]. However, results from iPrEX suggest that the decreases in BMD occur primarily during the first 24 weeks of prophylaxis with stabilization occurring thereafter. Fracture risk was very low with oral PrEP and appeared no greater in those receiving Truvada® than in placebo recipients in both iPrEX (1.7% versus 1.4%, respectively) and Partners PrEP (0.8% versus 0.6%, respectively) [Truvada® USPI, 2016].

Modest decreases in BMD following oral PrEP should be seen in the context of greater decreases in BMD from combination ART that is required to treat HIV infection, the effect of HIV infection on bone health, and the requirement for individuals with diagnosed HIV to take ART for life.

11.5 Drug interactions

Drug–drug interactions with Truvada® are described in detail in the Truvada® US Prescribing Information [Truvada® USPI, 2016]. In vitro studies and clinical pharmacokinetic drug–drug interaction trials have shown that the potential for cytochrome P450-mediated interactions involving emtricitabine and tenofovir with other medicinal products is low. No clinically significant drug interactions have been observed between FTC and famciclovir, indinavir, stavudine, TDF, and zidovudine. Similarly, no clinically significant drug interactions have been observed between TDF and efavirenz, methadone, nelfinavir, oral contraceptives, or ribavirin in trials conducted in healthy volunteers. The only clinically relevant drug interactions are with didanosine – where coadministration should be undertaken with caution, HIV-1 protease inhibitors, and adefovir dipivoxil. As these are antiretroviral agents used for treatment of HIV infection, it is unlikely that HIV uninfected individuals will be prescribed these drugs.
11.6 Summary of comparative safety

Truvada® has a well established safety profile from more than a decade of use as a first-line treatment for HIV-1 infection. However, giving antiretroviral agents to HIV uninfected individuals to avoid acquisition of HIV demands antiretroviral drugs that are exceptionally safe and well tolerated, especially as adherence to prophylactic medication is essential for effective protection.

As results from the RCTs and their open-label extensions have demonstrated, oral PrEP with Truvada® was generally well tolerated by trial participants. Adverse events that occurred significantly more frequently with Truvada® in comparison with placebo included nausea, headaches and weight loss but were self-limiting.

Rates of permanent discontinuation for adverse events were low across the RCTs and were similar for Truvada® and placebo. In iPrEX, for example, only 2% of study participants in the Truvada® arm permanently stopped taking PrEP, a rate similar to that seen among placebo recipients [Grant et al, 2010]. These findings suggest that safety of oral PrEP will not be a significant barrier to uptake. Studies that have looked at factors influencing the uptake of oral PrEP suggest that the safety and tolerability profile of Truvada® is unlikely to be a major factor affecting rates of uptake, adherence and persistence with oral PrEP [Young et al, 2014; Amico et al, 2014]. In the recently completed survey of PrEP use at the San Francisco Medical Center, less than 3% of individuals mentioned adverse events as a reason to not start taking PrEP [Volk et al, 2015].

A recent meta analysis of 18 trials revealed that adverse events were similar between PrEP and placebo groups. More cases of drug-resistant HIV infection were found among PrEP users who initiated PrEP while acutely HIV-infected, but incidence of acquiring drug-resistant HIV during PrEP use was low. Studies consistently found no association between PrEP use and changes in sexual risk behavior. PrEP was not associated with increased pregnancy-related adverse events or hormonal contraception effectiveness [Fonner VA et al, 2016].
12. Summary of available data on comparative cost and cost-effectiveness within the pharmacologic class or therapeutic group

12.1 Range of costs of the proposed medicine

12.1.1 USA

The US FDA approved Truvada® in July 2012 for once-daily oral PrEP in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk. The monthly cost of Truvada® tablets for PrEP varies among payers in the USA.

Table 5. Wholesale acquisition costs of Truvada® tablets in the USA

<table>
<thead>
<tr>
<th>Dosage form and product strength</th>
<th>Package size</th>
<th>Wholesale acquisition cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet containing:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg emtricitabine</td>
<td>30 tablets</td>
<td>$1466.44</td>
</tr>
<tr>
<td>300 mg tenofovir disoproxil fumarate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12.1.2 Developing countries

Gilead’s mission is to transform care for HIV and other life-threatening diseases throughout the world, to which end, our HIV treatment access effort has been based on the principle of tiered pricing of branded medicines based on a country’s ability to pay. Developing countries that are classified as low-income or lower-middle-income by World Bank, as well as those with significant unmet HIV disease burden, are designated as Access countries. Gilead’s no-profit price for a 30-day supply of oral PrEP with Truvada® to in-country Access Program distribution partners is US$ 20. Oral PrEP with Truvada® will be made available to Governments at this no-profit transfer price in addition to distribution and other related costs (these may vary from country to country).
12.2 Cost-effectiveness of oral PrEP with Truvada®

There is a growing body of data to indicate that oral PrEP with Truvada® can be both cost-effective and in certain situations cost-saving [WHO, 2012]. When used as prescribed, Truvada® prevents acquisition of HIV in people most at risk of HIV infection so avoiding the need for lifelong ART and its associated costs. Overall, data from RCTs and modelling simulations that have focused on PrEP use in low-income countries have demonstrated the following:

- A modelling exercise to assess the potential impact of PrEP in southern sub-Saharan Africa indicated significant public health benefit. Under a best case scenario up to 3.2 million new HIV-1 infections could be averted over a 10-year period by prescribing PrEP (with 90% effectiveness) to those at highest behavioral risk and by preventing sexual disinhibition [Abbas et al, 2007]

- A modelling exercise in the epidemiological settings of Botswana, Kenya and Southern India, which focused on sex workers and their clients, showed that oral PrEP was highly effective in African settings where HIV prevalence was relatively high and condom use more variable but less so in Southern India where prevalence was much lower and condom use high [Vissers et al, 2008]. PrEP would be most cost-effective in African settings due to the greater number of HIV infections averted.

- A study among young South African women (15–35 years), showed that targeted PrEP would prevent 10–25% of infections in the period 2014–2025 assuming a baseline incidence of 0.5% per year at 2025. The cost per HIV infection averted was between $12,500 and $20,000, depending on the level of ART coverage and baseline incidence [Pretorius et al, 2010]. This would be considered cost effective based on the WHO-CHOICE threshold.

- A study in serodiscordant heterosexual couples in South Africa, showed that providing PrEP to the uninfected partner was at least as cost-effective as initiating ART earlier in the infected partner. This was based on the assumption that the annual cost of PrEP was <40% of the annual cost of ART and PrEP was >70% effective [Hallett et al, 2011]

- Among high risk MSM and transgender women in Lima, Peru, a modelling exercise of oral PrEP (when downstream ART costs were included) proved cost-effective and was
only adversely impacted if there was a >80% reduction in condom use and PrEP efficacy fell below 40% [Gomez et al, 2012]

- Analyses from the Partners in Prevention RCT, which was carried out in Kenya and Uganda, showed that the cost of each HIV infection averted was between $6000 and $66,000 when PrEP was used as prescribed, with corresponding quality-adjusted life year (QALY) of $260 to $4900 [WHO, 2012]

- A modelling exercise of HIV infection among young women in KwaZulu-Natal, South Africa, where the risk for HIV acquisition is exceptionally high (6% annual incidence), showed that with PrEP targeted to 60% of 20–29-year-olds, in addition to baseline ART scale-up, incidence was reduced by 42% and 22% of infections averted at an additional $22,500 per infection averted. When targeted to 80% of high-risk individuals, PrEP reduced the incidence by 33% and averted 13% of infections at an additional $7400 per infection averted. PrEP coverage of 20% of the general population reduced incidence by 37% and incident infections by 18%, at an additional $26,900 per infection averted [Ying et al, 2013]

- A modelling exercise of South Africa’s adult population demonstrated that the greatest gains from PrEP come from targeted approaches that focus on individuals at higher risk of exposure to HIV rather than the general adult population and that in this setting it can be cost saving if PrEP effectiveness is above 10% [Alistar et al, 2014]

- A modelling exercise based on data from the Partner Demonstration Project of serodiscordant couples in Kampala, Uganda showed that over a 10-year period, incorporating PrEP into existing HIV testing and ART programmes would avert 43% of HIV infections with an incremental cost-effectiveness ratio (ICER) of $1340 per infection averted. This was judged as cost-effective as ART expansion alone, which would have led to 37% fewer HIV infections and an ICER of $1452 over the same period [Ying et al, 2015].

13. **Summary of regulatory status of the medicine**

At present, Truvada® is licensed for prevention of HIV infection in the US and on a named patient basis in France. Submissions are currently under review in Australia, Brazil, Thailand and it was recently approved in Canada. Because Truvada® is licensed for treatment of HIV-1
infection in the UK, Europe and Canada, it can be used off-label for prevention as post-exposure prophylaxis (PEP) in the UK and Europe and as PrEP in Canada and the UK.

• Botswana incorporated PrEP into its 2016 HIV Clinical Care Guidelines. Truvada for PrEP™ is technically, currently available in the private sector and will be publicly available and funded April 1, 2017

• PrEP is incorporated into the Kenyan HIV Prevention Revolution Roadmap and is also identified as an evidence-based intervention in the most recent Kenyan National Strategic Framework (KASF). Truvada® is also included as the preferred oral agent for PrEP in the Guidelines on use of ARV drugs for treating and preventing HIV Infections - 2016 edition

• In Malawi’s National HIV Prevention Strategy 2015–2020, PrEP is a stated part of the comprehensive prevention package for MSM and serodiscordant couples.

• The Peru Ministry of Health approved the use of fixed-dose combination of Truvada for PrEP™ in April 2016

• South Africa’s Medicines Control Council (MCC) approved the use of Truvada for PrEP™ in November 2015

• Zimbabwe AIDS prevention Program at the University of Zimbabwe has helped to move forward the discussion on PrEP access for serodiscordant couples, and helped ensure that couples counseling guidelines included specific information on helping HIV-negative individuals understand their risk. To adapt the HIV guidelines, the Ministry of Health has formed a committee with five subgroups, including one on PrEP

• NHS England and Public Health England will launch several test sites over the next two years to test cost-effectiveness and affordability of PrEP as part of an integrated HIV and STI prevention service

• The European Medicines Agency is in the process of reviewing Truvada for PrEP™. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union, but each member state will separately determine how, if at all, it might introduce them.

14. Availability of pharmacopoeial standards
(British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

14.1 Specifications of Truvada® tablets

British Pharmacopoeia: No standards available
International Pharmacopoeia: No standards available
US Pharmacopoeia: No standards available

15. Proposed (new/ adapted) text for the WHO Model Formulary

15.1 Other antivirals

Antiretrovirals
Fixed dose combinations
Tablet: 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate
Also known as Truvada®

*Uses:* Truvada® is licensed in the USA in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. While using Truvada for PrEP™, HIV-1 screening tests should be repeated at least every 3 months.

*Contraindications:* Do not use Truvada for PrEP™ in individuals with unknown or positive HIV-1 status or in patients with creatinine clearance <60 mL/min. Truvada® should be used in HIV-infected patients only in combination with other antiretroviral agents.

*Precautions:* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including Viread®, a component of Truvada®.

Truvada® is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued Truvada®. Therefore, hepatic function should be monitored closely.
in HBV-infected patients who discontinue Truvada®. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Prior to initiating Truvada for PrEP™, if clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm negative HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection. Hepatitis B status must be assessed and those who are not immune should be offered vaccination. Do not use with other tenofovir-containing products. Consider assessment of bone mineral density in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.

**Dose:** One tablet taken orally once daily, with or without food.

**Adverse effects:** In HIV-1 uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of Truvada® subjects and more frequently than by placebo subjects were headache, abdominal pain and weight decrease.

Please refer to the Prescribing Information appropriate to the Gilead Access Program contained in Appendix 1 for further details on Truvada®.
16. References


Grant RM et al. Benefits of pre-exposure prophylaxis relative to drug resistance risk AIDS 2016, Durban SA (TUAC0105LB)


Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016


National Institute for Health and Care Excellence. Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil)


Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016


Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016

Appendix 1. Access Prescribing Information for Truvada®

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TRUVADA® (emtricitabine/tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: 2004

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS, POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B, AND RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNIDENTIFIED EARLY HIV-1 INFECTION

See full prescribing information for complete boxed warning.

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients with no history of hepatitis B, C or HIV. Treatment should be promptly discontinued. (5.1)

- TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients coinfected with HIV-1 and HBV who have discontinued TRUVADA. Therefore, hepatic function should be monitored closely in HBV-infected patients who discontinue TRUVADA. If appropriate, initiation of anti-HBV therapy may be warranted. (5.2)

- TRUVADA used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initial use and periodically during use. Drug-resistant HIV-1 variants have been identified with the use of TRUVADA for a PrEP indication following an uninfected acute HIV-1 infection. Do not initiate TRUVADA for a PrEP indication if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed. (5.9)

---DOSE FORMS AND STRENGTHS---

Tablets: 200 mg/300 mg, 180 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg of emtricitabine and tenofovir disoproxil fumarate, respectively. (3)

---CONTRAINDICATIONS---

Do not use TRUVADA for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status. TRUVADA should be used in HIV-infected patients only in combination with other antiretroviral agents. (4)

---WARNINGS AND PRECAUTIONS---

- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess estimated creatinine clearance before initiating treatment with TRUVADA. In patients at risk for renal dysfunction, assess estimated creatinine clearance, serum potassium, urine glucose and urine protein before initiating treatment with TRUVADA and periodically during treatment. Avoid administering TRUVADA with concurrent or recent use of nephrotoxic drugs. (5.3)

- Contraindication with Other Products: Do not use with drugs containing emtricitabine, lamivudine, tenofovir, or tenofovir disoproxil fumarate including ATV, COMPLERA, EMTRIVA, GENVOYA, ODEFSEY, STIBILET, VIREAD, or with drugs containing lamivudine. Do not administer in combination with HEPSEDA. (5.4)

- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss. (5.5)

- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy. (6.1)

- Immune reconstitution syndrome: May necessitate further evaluation and treatment. (6.2)

---RECENT MAJOR CHANGES---

<table>
<thead>
<tr>
<th>Indications and Usage</th>
<th>03/2016</th>
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</thead>
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<tr>
<td>Treatment of HIV-1 infection (1.1)</td>
<td>03/2016</td>
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<tr>
<td>Dosage and Administration (2.2)</td>
<td>03/2016</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>03/2016</td>
</tr>
<tr>
<td>Coadministration with Other Products (5.4)</td>
<td>03/2016</td>
</tr>
</tbody>
</table>
Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016

INDICATIONS AND USAGE
TRUVADA is a combination of EMTRIVA and VIREAD, both nucleoside analog HIV-1 reverse transcriptase inhibitors. TRUVADA 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. (1) TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. (1)

DOSAGE AND ADMINISTRATION

Treatment of HIV-1 infection (2.1)

- Recommended dose in adults and pediatric patients weighing greater than or equal to 55 kg: One TRUVADA tablet (containing 200 mg/300 mg of emtricitabine and tenofovir disoproxil fumarate) once daily taken orally with or without food. (2.1)
- Recommended dose in pediatric patients weighing greater than or equal to 17 kg and able to swallow a whole tablet: One TRUVADA low strength tablet (100 mg/150 mg, 135 mg/200 mg, or 157 mg/250 mg based on body weight) once daily taken orally with or without food. (2.2)
- Recommended dose in renal impairment: In HIV-1 infected adult patients. Creatinine clearance 30-49 mL/min: 1 tablet every 48 hours. (2.4) CI/Cr below 30 mL/min or hemodialysis: Do not use TRUVADA. (2.4)

Pre-exposure Prophylaxis (2.2)

- Recommended dose in HIV-1 uninfected adults: One tablet (containing 200 mg/300 mg of emtricitabine and tenofovir)

DRUG INTERACTIONS

- Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted. (7.1)

- HIV-1 protease inhibitors: Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. When coadministered with TRUVADA, use atazanavir given with

ADVERSE REACTIONS

In HIV-1 infected patients, the most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. (6.1)

In HIV-1 uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of TRUVADA subjects and more frequently than placebo subjects were headache, abdominal pain, weight decreased. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-888-443-5255 or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch

Use in Specific Populations

- Nursing mothers: Women infected with HIV-1 should be instructed not to breastfeed. (3.2)

See 17 for Patient Counseling Information and Medication Guide.

Revised 04/2016
FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS, POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B, and RISK OF DRUG RESISTANCE WITH USE OF TRUVADA FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA, in combination with other antiretrovirals [see Warnings and Precautions (5.1)].

TRUVADA is not approved for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of TRUVADA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued TRUVADA. Therefore, hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted [see Warnings and Precautions (5.2)].

TRUVADA used for a PrEP indication must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and periodically (at least every 3 months) during use. Drug-resistant HIV-1 variants have been identified with use of TRUVADA for a PrEP indication following undetected acute HIV-1 infection. Do not initiate TRUVADA for a PrEP indication if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed [see Warnings and Precautions (5.9)].
1 INDICATIONS AND USAGE

1.1 Treatment of HIV-1 Infection

TRUVADA®, a combination of EMTRIVA® and VIREAD®, 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 [see Dosage and Administration (2) and Clinical Studies (14)].

The following points should be considered when initiating therapy with TRUVADA for the treatment of HIV-1 infection:

- It is not recommended that TRUVADA be used as a component of a triple nucleoside regimen.
- TRUVADA should not be coadministered with ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, VIREAD or lamivudine-containing products [see Warnings and Precautions (5.4)].
- In treatment experienced patients, the use of TRUVADA should be guided by laboratory testing and treatment history [see Microbiology (12.4)].
1.2 Pre-Exposure Prophylaxis

TRUVADA is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples [see Clinical Studies (14.2, 14.3)].

When considering TRUVADA for pre-exposure prophylaxis the following factors may help to identify individuals at high risk:
- has partner(s) known to be HIV-1 infected, or
- engages in sexual activity within a high prevalence area or social network and one or more of the following:
  - inconsistent or no condom use
  - diagnosis of sexually transmitted infections
  - exchange of sex for commodities (such as money, food, shelter, or drugs)
  - use of illicit drugs or alcohol dependence
  - incarceration
  - partner(s) of unknown HIV-1 status with any of the factors listed above

When prescribing TRUVADA for pre-exposure prophylaxis, healthcare providers must:
- prescribe TRUVADA as part of a comprehensive prevention strategy because TRUVADA is not always effective in preventing the acquisition of HIV-1 infection [see Warnings and Precautions (5.9)];
- counsel all uninfected individuals to strictly adhere to the recommended TRUVADA dosing schedule because the effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 was strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials [see Warnings and Precautions (5.9)];
- confirm a negative HIV-1 test immediately prior to initiating TRUVADA for a PrEP indication. If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection [see Warnings and Precautions (5.9)]; and
- screen for HIV-1 infection at least once every 3 months while taking TRUVADA for PrEP.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose for Treatment of HIV-1 Infection in Adults and Pediatric Patients Weighing 35 Kg or More

The recommended dose of TRUVADA in adults and in pediatric patients with body weight greater than or equal to 35 kg is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.
2.2 Recommended Dose for Treatment of HIV-1 Infection in Pediatric Patients Weighing at Least 17 kg and Able to Swallow a Whole Tablet

The recommended oral dose for pediatric patients weighing greater than or equal to 17 kg and who are able to swallow a whole tablet, is one TRUVADA low strength tablet (emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) (167 mg/250 mg, 133 mg/200 mg, or 100 mg/150 mg based on body weight) taken orally once daily with or without food.

The recommended oral dosage of TRUVADA low strength tablets is presented in Table 1. Weight should be monitored periodically and the TRUVADA dose adjusted accordingly.

Table 1 Dosing for Pediatric Patients Weighing 17 kg to less than 35 kg using TRUVADA Low Strength Tablets

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dosing of FTC (mg)/TDF (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 to less than 22</td>
<td>one 100/150 tablet once daily</td>
</tr>
<tr>
<td>22 to less than 28</td>
<td>one 133/200 tablet once daily</td>
</tr>
<tr>
<td>28 to less than 35</td>
<td>one 167/250 tablet once daily</td>
</tr>
</tbody>
</table>

2.3 Recommended Dose for Pre-exposure Prophylaxis

The dose of TRUVADA in HIV-1 uninfected adults is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate) once daily taken orally with or without food.

2.4 Dose Adjustment for Renal Impairment

Treatment of HIV-1 Infection

Significantly increased drug exposures occurred when EMTRIVA or VIREAD were administered to subjects with moderate to severe renal impairment [see EMTRIVA or VIREAD Package Insert]. Therefore, adjust the dosing interval of TRUVADA in HIV-1 infected adult patients with baseline creatinine clearance 30–49 mL/min using the recommendations in Table 2. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV infected subjects. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients [see Warnings and Precautions (5.3)].

No dose adjustment is necessary for HIV-1 infected patients with mild renal impairment (creatinine clearance 50–80 mL/min). No data are available to make dose recommendations in pediatric patients with renal impairment.
### Table 2  Dosage Adjustment for HIV-1 Infected Adult Patients with Altered Creatinine Clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)(^a)</th>
<th>≥50</th>
<th>30–49</th>
<th>&lt;30 (Including Patients Requiring Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended Dosing Interval</td>
<td>Every 24 hours</td>
<td>Every 48 hours</td>
<td>TRUVADA should not be administered.</td>
</tr>
</tbody>
</table>

\(a\). Calculated using ideal (lean) body weight

Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in all individuals with mild renal impairment [see Warnings and Precautions (5.3)].

**Pre-exposure Prophylaxis**

Do not use TRUVADA for a PrEP indication in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min [see Warnings and Precautions (5.3)].

Routine monitoring of estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein should be performed in all individuals with mild renal impairment. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use [see Warnings and Precautions (5.3)].

### 3 DOSAGE FORMS AND STRENGTHS

TRUVADA tablets are available in four dose strengths:

- Tablet: 100 mg of emtricitabine and 150 mg of tenofovir disoproxil fumarate (equivalent to 123 mg of tenofovir disoproxil): blue, oval-shaped, film-coated, debossed with “GSI” on one side and with “703” on the other side.

- Tablet: 133 mg of emtricitabine and 200 mg of tenofovir disoproxil fumarate (equivalent to 163 mg of tenofovir disoproxil): blue, rectangular-shaped, film-coated, debossed with “GSI” on one side and with “704” on the other side.

- Tablet: 167 mg of emtricitabine and 250 mg of tenofovir disoproxil fumarate (equivalent to 204 mg of tenofovir disoproxil): blue, modified capsule-shaped, film-coated, debossed with “GSI” on one side and with “705” on the other side.

- Tablet: 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil): blue, capsule-shaped, film-coated, debossed with “GILEAD” on one side and with “701” on the other side.
4 CONTRAINDICATIONS

Do not use TRUVADA for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status. TRUVADA should be used in HIV-infected patients only in combination with other antiretroviral agents.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including VIREAD, a component of TRUVADA, 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 or uninfected individual with known risk factors for liver disease; however, cases have also been reported in HIV-1 infected patients with no known risk factors. Treatment with TRUVADA should be suspended in any patient or uninfected individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

5.2 HBV Infection

It is recommended that all individuals be tested for the presence of chronic hepatitis B virus (HBV) before initiating TRUVADA. TRUVADA is not approved for the treatment of chronic HBV infection and the safety and efficacy of TRUVADA have not been established in patients infected with HBV. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV-1 and have discontinued TRUVADA. In some patients infected with HBV and treated with EMTRIVA, the exacerbations of hepatitis B were associated with liver decompensation and liver failure. Patients who are infected with HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with TRUVADA. If appropriate, initiation of anti-hepatitis B therapy may be warranted. HBV-uninfected individuals should be offered vaccination.

5.3 New Onset or Worsening Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of VIREAD [see Adverse Reactions (6.3)].

It is recommended that estimated creatinine clearance be assessed in all individuals prior to initiating therapy and as clinically appropriate during therapy with TRUVADA. In patients at risk of renal dysfunction, including patients who have previously experienced renal events while receiving HEPSERA®, it is recommended that estimated creatinine clearance, serum phosphorus, urine glucose, and urine protein be assessed prior to initiation of TRUVADA, and periodically during TRUVADA therapy.

TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs)) [see Drug
Interactions (7.4)]. Cases of acute renal failure after initiation of high dose or multiple NSAIDs have been reported in HIV-infected patients with risk factors for renal dysfunction who appeared stable on tenofovir disoproxil fumarate (tenofovir DF). Some patients required hospitalization and renal replacement therapy. Alternatives to NSAIDs should be considered, if needed, in patients at risk for renal dysfunction.

Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients.

Treatment of HIV-1 Infection

Dosing interval adjustment of TRUVADA and close monitoring of renal function are recommended in all patients with estimated creatinine clearance 30–49 mL/min [see Dosage and Administration (2.4)]. No safety or efficacy data are available in patients with renal impairment who received TRUVADA using these dosing guidelines, so the potential benefit of TRUVADA therapy should be assessed against the potential risk of renal toxicity. TRUVADA should not be administered to patients with estimated creatinine clearance below 30 mL/min or patients requiring hemodialysis.

Pre-exposure Prophylaxis

TRUVADA for a PrEP indication should not be used if estimated creatinine clearance is less than 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use [see Dosage and Administration (2.4)].

5.4 Coadministration with Other Products

TRUVADA is a fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate. Do not coadminister TRUVADA with other drugs containing emtricitabine or tenofovir disoproxil fumarate, or containing tenofovir alafenamide, including ATRIPLA, COMPLERA, EMTRIVA, GENVOYA, ODEFSEY, STRIBILD, or VIREAD. Due to similarities between emtricitabine and lamivudine, do not coadminister TRUVADA with other drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Dutrebis (lamivudine/raltegravir), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Triumeq (abacavir sulfate/dolutegravir/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine).

Do not coadminister TRUVADA with HEPSERA (adefovir dipivoxil).

5.5 Bone Effects of Tenofovir DF

Bone Mineral Density:

In clinical trials in HIV-1 infected adults and in a clinical trial of HIV-1 uninfected individuals, tenofovir DF was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators [see Adverse Reactions (6.2) and VIREAD prescribing information]. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving tenofovir DF.
Clinical trials evaluating tenofovir DF in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the tenofovir DF treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. For more information, consult the VIREAD prescribing information.

The effects of tenofovir DF-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adult and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of tenofovir DF [see Adverse Reactions (6.3)]. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF [see Warnings and Precautions (5.3)].

5.6 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in HIV-1 infected patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.7 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in HIV-1 infected patients treated with combination antiretroviral therapy, including TRUVADA. During the initial phase of combination antiretroviral treatment, HIV-1 infected patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment.

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

Clinical trials in HIV-1 infected subjects have demonstrated that certain regimens that only contain three nucleoside reverse transcriptase inhibitors (NRTI) are generally less effective than triple drug regimens containing two NRTIs in combination with either a non-nucleoside reverse transcriptase inhibitor or a HIV-1 protease inhibitor. In particular, early virologic failure and high rates of resistance substitutions have been reported. Triple nucleoside regimens should therefore be used with caution. Patients on a therapy utilizing a triple nucleoside-only regimen should be carefully monitored and considered for treatment modification.

5.9 Comprehensive Management to Reduce the Risk of Acquiring HIV-1

Use TRUVADA for pre-exposure prophylaxis only as part of a comprehensive prevention strategy that includes other prevention measures, such as safer sex practices, because TRUVADA is not always effective in preventing the acquisition of HIV-1 [see Clinical Studies (14.2 and 14.3)].

- Counsel uninfected individuals about safer sex practices that include consistent and correct use of condoms, knowledge of their HIV-1 status and that of their partner(s), and regular testing for other sexually transmitted infections that can facilitate HIV-1 transmission (such as syphilis and gonorrhea).

- Inform uninfected individuals about and support their efforts in reducing sexual risk behavior.

Use TRUVADA to reduce the risk of acquiring HIV-1 only in individuals confirmed to be HIV-negative. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only TRUVADA, because TRUVADA alone does not constitute a complete treatment regimen for HIV-1 treatment [see Microbiology (12.4)]; therefore, care should be taken to minimize drug exposure in HIV-infected individuals.

- Many HIV-1 tests, such as rapid tests, detect anti-HIV antibodies and may not identify HIV-1 during the acute stage of infection. Prior to initiating TRUVADA for a PrEP indication, evaluate seronegative individuals for current or recent signs or symptoms consistent with acute viral infections (e.g., fever, fatigue, myalgia, skin rash, etc.) and ask about potential exposure events (e.g., unprotected, or condom broke during sex with an HIV-1 infected partner) that may have occurred within the last month.

  - If clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

- While using TRUVADA for a PrEP indication, HIV-1 screening tests should be repeated at least every 3 months. If symptoms consistent with acute HIV-1 infection develop following a potential exposure event, PrEP should be discontinued until negative infection status is confirmed using a test approved by
the FDA as an aid in the diagnosis of HIV-1, including acute or primary HIV-1 infection.

Counsel uninfected individuals to strictly adhere to the recommended TRUVADA dosing schedule. The effectiveness of TRUVADA in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in clinical trials [see Clinical Studies (14.2 and 14.3)].

6 ADVERSE REACTIONS

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

- Lactic Acidosis/Severe Hepatomegaly with Steatosis [see Boxed Warning, Warnings and Precautions (5.1)].
- Severe Acute Exacerbations of hepatitis B [see Boxed Warning, Warnings and Precautions (5.2)].
- New Onset or Worsening Renal Impairment [see Warnings and Precautions (5.3)].
- Bone Effects of Tenofovir DF [see Warnings and Precautions (5.5)].
- Immune Reconstitution Syndrome [see Warnings and Precautions (5.7)].

6.1 Adverse Reactions from Clinical Trials Experience in HIV-1 Infected Subjects

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

Clinical Trials in Adult Subjects

The most common adverse reactions (incidence greater than or equal to 10%, any severity) occurring in Study 934, an active-controlled clinical trial of efavirenz, emtricitabine, and tenofovir disoproxil fumarate, include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash. See also Table 3 for the frequency of treatment-emergent adverse reactions (Grades 2–4) occurring in greater than or equal to 5% of subjects treated in any treatment group in this trial.

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

Study 934 - Treatment Emergent Adverse Reactions: In Study 934, 511 antiretroviral-naïve subjects received either VIREAD + EMTRIVA administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254) for 144 weeks. Subjects had a mean age of 40 years (range 20 to 73 years) and were predominantly male (88%). Overall, 65% were White, 17% were Black, and 13% were Hispanic. Adverse reactions observed in this trial were generally consistent with those seen in other trials in treatment-experienced or treatment-naïve subjects receiving VIREAD and/or EMTRIVA (Table 3).
### Table 3 Selected Treatment-Emergent Adverse Reactions<sup>a</sup> (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 934 (0–144 Weeks)

<table>
<thead>
<tr>
<th>Category</th>
<th>FTC+TDF+EFV&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AZT/3TC+EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=257</td>
<td>N=254</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash event&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7%</td>
<td>9%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Frequencies of adverse reactions are based on all treatment-emergent adverse events, regardless of relationship to study drug.

<sup>b</sup> From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

<sup>c</sup> Rash event includes rash, exfoliative rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and rash vesicular.

**Laboratory Abnormalities:** Laboratory abnormalities observed in this trial were generally consistent with those seen in other trials of VIREAD and/or EMTRIVA (Table 4).
Table 4  Significant Laboratory Abnormalities Reported in ≥1% of Subjects in Any Treatment Group in Study 934 (0–144 Weeks)

<table>
<thead>
<tr>
<th></th>
<th>FTC+TDF+EFV&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AZT/3TC+EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=257</td>
<td>N=254</td>
</tr>
<tr>
<td>Any ≥ Grade 3 Laboratory Abnormality</td>
<td>30%</td>
<td>26%</td>
</tr>
<tr>
<td>Fasting Cholesterol (&gt;240 mg/dL)</td>
<td>22%</td>
<td>24%</td>
</tr>
<tr>
<td>Creatine Kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(M: &gt;990 U/L)</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>(F: &gt;845 U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Amylase (&gt;175 U/L)</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Alkaline Phosphatase (&gt;550 U/L)</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>AST (M: &gt;180 U/L)</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>(F: &gt;170 U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (M: &gt;215 U/L)</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>(F: &gt;170 U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (&lt;8.0 mg/dL)</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Hyperglycemia (&gt;250 mg/dL)</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Hematuria (&gt;75 RBC/HPF)</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Glycosuria (≥3+)</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Neutrophils (&lt;750/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Fasting Triglycerides (&gt;750 mg/dL)</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<sup>a</sup> From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of VIREAD + EMTRIVA with efavirenz.

In addition to the events described above for Study 934, other adverse reactions that occurred in at least 5% of subjects receiving EMTRIVA or VIREAD with other antiretroviral agents in clinical trials include anxiety, arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, and rhinitis.

In addition to the laboratory abnormalities described above for Study 934, Grades 3-4 laboratory abnormalities of increased bilirubin (>2.5 x ULN), increased pancreatic amylase (>2.0 x ULN), increased or decreased serum glucose (<40 or >250 mg/dL), and increased serum lipase (>2.0 x ULN) occurred in up to 3% of subjects treated with EMTRIVA or VIREAD with other antiretroviral agents in clinical trials.

Clinical Trials in Pediatric Subjects

Emtricitabine: In addition to the adverse reactions reported in adults, anemia and hyperpigmentation were observed in 7% and 32%, respectively, of pediatric subjects (3 months to less than 18 years of age) who received treatment with EMTRIVA in the
larger of two open-label, uncontrolled pediatric trials (N=116). For additional information, consult the EMTRIVA prescribing information.

_Tenofvir Disoproxil Fumarate:_ In pediatric clinical trials (Studies 352 and 321) conducted in 184 HIV-1 infected subjects 2 to less than 18 years of age, the adverse reactions observed in pediatric subjects who received treatment with VIREAD were consistent with those observed in clinical trials of VIREAD in adults.

Eighty-nine pediatric subjects (2 to less than 12 years of age) received VIREAD in Study 352 for a median exposure of 104 weeks. Of these, 4 subjects discontinued from the trial due to adverse reactions consistent with proximal renal tubulopathy. Three of these 4 subjects presented with hypophosphatemia and also had decreases in total body or spine BMD Z score [see Warnings and Precautions (5.5)]. For additional information, consult the VIREAD prescribing information.

**6.2 Adverse Reactions from Clinical Trial Experience in HIV-1 Uninfected Adult Subjects**

No new adverse reactions to TRUVADA were identified from two randomized placebo-controlled clinical trials (iPrEx, Partners PrEP), in which 2,830 HIV-1 uninfected adults received TRUVADA once daily for pre-exposure prophylaxis. Subjects were followed for a median of 71 weeks and 87 weeks, respectively. These trials enrolled HIV-negative individuals ranging in age from 18 to 67 years. The iPrEx trial enrolled only men or transgender women of Hispanic/Latino (72%), White (18%), Black (9%) and Asian (5%) race. The Partners PrEP trial enrolled both men (61-64% across treatment groups) and women in Kenya and Uganda. Table 5 provides a list of all adverse events that occurred in 2% or more of subjects in any treatment group in the iPrEx and Partners PrEP trials.

_Laboratory Abnormalities:_ Table 6 provides a list of laboratory abnormalities observed in both trials. Six subjects in the TDF-containing arms of the Partners PrEP trial discontinued participation in the study due to an increase in blood creatinine compared with no discontinuations in the placebo group. One subject in the TRUVADA arm of the iPrEx trial discontinued from the study due to an increase in blood creatinine and another due to low phosphorous.

In addition to the laboratory abnormalities described above, Grade 1 proteinuria (1+) occurred in 6% of subjects receiving TRUVADA in the iPrEx trial. Grades 2-3 proteinuria (2–4+) and glycosuria (3+) occurred in less than 1% of subjects treated with TRUVADA in the iPrEx trial and Partners PrEP trial.
Table 5  Selected Adverse Events (All Grades) Reported in ≥2% in Any Treatment Group in the iPrEx Trial and Partners PrEP Trial

<table>
<thead>
<tr>
<th></th>
<th>iPrEx Trial</th>
<th></th>
<th>Partners PrEP Trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTC/TDF</td>
<td>Placebo N=1248</td>
<td>FTC/TDF N=1579</td>
<td>Placebo N=1584</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>8%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4%</td>
<td>2%</td>
<td>-(^a)</td>
<td>-</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>13%</td>
<td>16%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urethritis</td>
<td>5%</td>
<td>7%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Syphilis</td>
<td>6%</td>
<td>5%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Secondary syphilis</td>
<td>6%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anogenital warts</td>
<td>2%</td>
<td>3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>5%</td>
<td>5%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7%</td>
<td>6%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>6%</td>
<td>7%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3%</td>
<td>3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital ulceration</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>3%</td>
<td>2%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a. Not reported or reported below 2%.
Table 6  Laboratory Abnormalities (Highest Toxicity Grade) Reported for Each Subject in the iPrEx Trial and Partners PrEP Trial

<table>
<thead>
<tr>
<th>Grade</th>
<th>Creatinine</th>
<th>Phosphorus</th>
<th>AST</th>
<th>ALT</th>
<th>Hemoglobin</th>
<th>Neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTC/TDF (N= 1251)</td>
<td>Placebo (N= 1248)</td>
<td>FTC/TDF (N=1579)</td>
<td>Placebo (N=1584)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(1.1–1.3 X ULN)</td>
<td>27 (2%)</td>
<td>21 (2%)</td>
<td>18 (1%)</td>
<td>12 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>(&gt; 1.4 x ULN)</td>
<td>5 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(2.5 – &lt;LLN mg/dL)</td>
<td>81 (7%)</td>
<td>110 (9%)</td>
<td>NR a</td>
<td>NR a</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>(&lt;2.0 mg/dL)</td>
<td>123 (10%)</td>
<td>101 (8%)</td>
<td>140 (9%)</td>
<td>136 (9%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(1.25–&lt;2.5 x ULN)</td>
<td>175 (14%)</td>
<td>175 (14%)</td>
<td>20 (1%)</td>
<td>25 (2%)</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>(&gt; 2.6 x ULN)</td>
<td>57 (5%)</td>
<td>61 (5%)</td>
<td>10 (&lt;1%)</td>
<td>4 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(1.25–&lt;2.5 x ULN)</td>
<td>178 (14%)</td>
<td>194 (16%)</td>
<td>21 (1%)</td>
<td>13 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>(&gt; 2.6 x ULN)</td>
<td>84 (7%)</td>
<td>82 (7%)</td>
<td>4 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(8.5 – 10 mg/dL)</td>
<td>49 (4%)</td>
<td>62 (5%)</td>
<td>56 (4%)</td>
<td>39 (2%)</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>(&lt;9.4 mg/dL)</td>
<td>13 (1%)</td>
<td>19 (2%)</td>
<td>28 (2%)</td>
<td>39 (2%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(1000–1300/mm³)</td>
<td>23 (2%)</td>
<td>25 (2%)</td>
<td>208 (13%)</td>
<td>163 (10%)</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>(&lt;750/mm³)</td>
<td>7 (&lt;1%)</td>
<td>7 (&lt;1%)</td>
<td>73 (5%)</td>
<td>56 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

a. Grade 1 phosphorus was not reported for the Partners PrEP trial.
b. Grading is per DAIDS criteria.

Changes in Bone Mineral Density:

In clinical trials of HIV-1 uninfected individuals, decreases in BMD were observed. In the iPrEx trial, a substudy of 503 subjects found mean changes from baseline in BMD ranging from –0.4% to –1.0% across total hip, spine, femoral neck, and trochanter in the TRUVADA group compared with the placebo group, which returned toward baseline after discontinuation of treatment. Thirteen percent of subjects receiving TRUVADA versus 6% of subjects receiving placebo lost at least 5% of BMD at the spine during treatment. Bone fractures were reported in 1.7% of the TRUVADA group compared with 1.4% in the placebo group. No correlation between BMD and fractures was noted [see Clinical Studies (14.2)]. The Partners PrEP trial found similar fracture rates between treatment and placebo groups (0.8% and 0.6%, respectively). No BMD evaluations were performed during this trial [see Clinical Studies (14.3)].

6.3  Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VIREAD. No additional adverse reactions have been identified during postapproval use of EMTRIVA. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Immune System Disorders
allergic reaction, including angioedema

Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders
dyspnea

Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders
rash

Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

General Disorders and Administration Site Conditions
asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

7 DRUG INTERACTIONS

No drug interaction trials have been conducted using TRUVADA tablets. Drug interaction trials have been conducted with emtricitabine and tenofovir disoproxil fumarate, the components of TRUVADA. This section describes clinically relevant drug interactions observed with emtricitabine and tenofovir disoproxil fumarate [see Clinical Pharmacology (12.3)].

7.1 Didanosine

Coadministration of TRUVADA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions.

When tenofovir disoproxil fumarate was administered with didanosine the Cmax and AUC of didanosine increased significantly [see Clinical Pharmacology (12.3)]. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and
neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving tenofovir DF with didanosine 400 mg daily.

In patients weighing greater than 60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, TRUVADA and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).

7.2 HIV-1 Protease Inhibitors

Tenofovir decreases the AUC and C_{min} of atazanavir [see Clinical Pharmacology (12.3)]. When coadministered with TRUVADA, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. TRUVADA should not be coadministered with atazanavir without ritonavir.

Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir have been shown to increase tenofovir concentrations [see Clinical Pharmacology (12.3)]. Tenofovir disoproxil fumarate is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters. When tenofovir disoproxil fumarate is co-administered with an inhibitor of these transporters, an increase in absorption may be observed. Patients receiving TRUVADA concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir should be monitored for tenofovir disoproxil fumarate-associated adverse reactions. TRUVADA should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse reactions.

7.3 Hepatitis C Antiviral Agents

Coadministration of tenofovir disoproxil fumarate and HARVONI® (ledipasvir/sofosbuvir) has been shown to increase tenofovir exposure [see Clinical Pharmacology (12.3)].

In patients receiving TRUVADA concomitantly with HARVONI without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

In patients receiving TRUVADA concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with tenofovir disoproxil fumarate.

7.4 Drugs Affecting Renal Function

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion [see Clinical Pharmacology (12.3)]. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of TRUVADA with drugs that are eliminated by active tubular secretion may increase concentrations of emtricitabine, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs [see Warnings and Precautions (5.3)].
Drugs that decrease renal function may increase concentrations of emtricitabine and/or tenofovir.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

Risk Summary

TRUVADA has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

Clinical Considerations

As of July 2011, the APR has received prospective reports of 764 and 1,219 exposures to emtricitabine- and tenofovir-containing regimens, respectively in the first trimester, 321 and 455 exposures, respectively, in second trimester, and 140 and 257 exposures, respectively, in the third trimester. Birth defects occurred in 18 of 764 (2.4%) live births for emtricitabine-containing regimens and 27 of 1219 (2.2%) live births for tenofovir-containing regimens (first trimester exposure) and 10 of 461 (2.2%) live births for emtricitabine-containing regimens and 15 of 714 (2.1%) live births for tenofovir-containing regimens (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between emtricitabine or tenofovir and overall birth defects observed in the APR.

Animal Data

Emtricitabine:

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.

Tenofovir Disoproxil Fumarate:

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.
8.3 Nursing Mothers

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1.

Studies in humans have shown that both tenofovir and emtricitabine are excreted in human milk. Because the risks of low level exposure to emtricitabine and tenofovir to infants are unknown, mothers should be instructed not to breast-feed if they are receiving TRUVADA, whether they are taking TRUVADA for treatment or to reduce the risk of acquiring HIV-1.

Emtricitabine

Samples of breast milk obtained from five HIV-1 infected mothers show that emtricitabine is secreted in human milk. Breastfeeding infants whose mothers are being treated with emtricitabine may be at risk for developing viral resistance to emtricitabine. Other emtricitabine-associated risks in infants breastfed by mothers being treated with emtricitabine are unknown.

Tenofovir Disoproxil Fumarate

Samples of breast milk obtained from five HIV-1 infected mothers show that tenofovir is secreted in human milk. Tenofovir-associated risks, including the risk of viral resistance to tenofovir, in infants breastfed by mothers being treated with tenofovir disoproxil fumarate are unknown.

8.4 Pediatric Use

No pediatric clinical trial was conducted to evaluate the safety and efficacy of TRUVADA. Data from previously conducted trials with the individual drug products, EMTRIVA and VIREAD, were relied upon to support dosing recommendations for TRUVADA. For additional information, consult the prescribing information for EMTRIVA and VIREAD.

TRUVADA should only be administered to HIV-1 infected pediatric patients with body weight greater than or equal to 17 kg and who are able to swallow a whole tablet. Because it is a fixed-dose combination tablet, TRUVADA cannot be adjusted for patients of lower weight [see Warnings and Precautions (5.5), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]. TRUVADA has not been evaluated for use in pediatric patients weighing less than 17 kg.

8.5 Geriatric Use

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

8.6 Patients with Impaired Renal Function

Treatment of HIV-1 Infection

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The dosing interval for TRUVADA should be modified in HIV-infected adult patients with estimated creatinine clearance of 30–49 mL/min. TRUVADA should not be used in patients with estimated creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis [see Dosage and Administration (2.4)].

Pre-exposure Prophylaxis

TRUVADA for a PrEP indication should not be used in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use [see Dosage and Administration (2.4)].

10 OVERDOSAGE

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

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

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

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In one trial, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of VIREAD, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

11 DESCRIPTION

TRUVADA tablets are fixed-dose combination tablets containing emtricitabine and tenofovir disoproxil fumarate. Emtricitabine is a synthetic nucleoside analog of cytidine. Tenofovir DF is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5’-monophosphate. Both emtricitabine and tenofovir exhibit inhibitory activity against HIV-1 reverse transcriptase.

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

It has a molecular formula of C8H10FN3O3S and a molecular weight of 247.24. It has the following structural formula:
Emtricitabine is a white to off-white crystalline powder with a solubility of 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.

**Tenofovir Disoproxil Fumarate:** Tenofovir disoproxil fumarate is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2 [[bis[[isopropoxycarbonyl]oxy]-methoxy]phosphinyl][methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of C_{19}H_{30}N_{5}O_{10}P • C_{4}H_{4}O_{4} and a molecular weight of 635.52. It has the following structural formula:

![Tenofovir Disoproxil Fumarate Structure](image)

Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25 °C. The partition coefficient (log p) for tenofovir disoproxil is 1.25 and the pKa is 3.75. All dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

**TRUVADA** tablets are for oral administration, and are available in the following strengths:

- Film-coated tablet containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 167 mg of emtricitabine and 250 mg of tenofovir disoproxil fumarate (which is equivalent to 204 mg of tenofovir disoproxil) as active ingredients
- Film-coated tablet containing 133 mg of emtricitabine and 200 mg of tenofovir disoproxil fumarate (which is equivalent to 163 mg of tenofovir disoproxil) as active ingredients
• Film-coated tablet containing 100 mg of emtricitabine and 150 mg of tenofovir disoproxil fumarate (which is equivalent to 123 mg of tenofovir disoproxil) as active ingredients

All strength of TRUVADA tablets also include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch (gluten free). The 200 mg/300 mg strength tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The 167 mg/250 mg, 133 mg/200 mg, and 100 mg/150 mg strength tablets are coated with Opadry II Blue, which contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

For additional information on Mechanism of Action, Antiviral Activity, Resistance and Cross Resistance, consult the EMTRIVA and VIREAD prescribing information.

12.1 Mechanism of Action

TRUVADA is a fixed-dose combination of antiviral drugs emtricitabine and tenofovir disoproxil fumarate [see Microbiology (12.4)].

12.3 Pharmacokinetics

TRUVADA: One TRUVADA tablet was bioequivalent to one EMTRIVA capsule (200 mg) plus one VIREAD tablet (300 mg) following single-dose administration to fasting healthy subjects (N=39).

Emtricitabine: The pharmacokinetic properties of emtricitabine are summarized in Table 7. Following oral administration of EMTRIVA, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Less than 4% of emtricitabine binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.02–200 μg/mL. Following administration of radiolabelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of EMTRIVA, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 7. Following oral administration of VIREAD, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01–25 μg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours.
Table 7  Single Dose Pharmacokinetic Parameters for Emtricitabine and Tenofovir in Adults\textsuperscript{a}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Emtricitabine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted Oral Bioavailability\textsuperscript{b} (%)</td>
<td>92 (83.1–106.4)</td>
<td>25 (NC–45.0)</td>
</tr>
<tr>
<td>Plasma Terminal Elimination Half-Life\textsuperscript{b} (hr)</td>
<td>10 (7.4–18.0)</td>
<td>17 (12.0–25.7)</td>
</tr>
<tr>
<td>$C_{\text{max}}$\textsuperscript{c} ($\mu$g/mL)</td>
<td>1.8±0.72\textsuperscript{d}</td>
<td>0.30±0.09</td>
</tr>
<tr>
<td>AUC\textsuperscript{c} ($\mu$g·hr/mL)</td>
<td>10.0±3.12\textsuperscript{d}</td>
<td>2.29±0.69</td>
</tr>
<tr>
<td>$CL/F$\textsuperscript{c} (mL/min)</td>
<td>302±94</td>
<td>1043±115</td>
</tr>
<tr>
<td>$CL_{\text{renal}}$\textsuperscript{c} (mL/min)</td>
<td>213±89</td>
<td>243±33</td>
</tr>
</tbody>
</table>

\textsuperscript{a} NC=Not calculated
\textsuperscript{b} Median (range)
\textsuperscript{c} Mean (± SD)
\textsuperscript{d} Data presented as steady state values

**Effects of Food on Oral Absorption**

TRUVADA may be administered with or without food. Administration of TRUVADA following a high fat meal (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir $C_{\text{max}}$ by approximately 0.75 hour. The mean increases in tenofovir AUC and $C_{\text{max}}$ were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy trials, VIREAD (tenofovir) was taken under fed conditions. Emtricitabine systemic exposures (AUC and $C_{\text{max}}$) were unaffected when TRUVADA was administered with either a high fat or a light meal.

**Special Populations**

**Race**

*Emtricitabine:* No pharmacokinetic differences due to race have been identified following the administration of EMTRIVA.

*Tenofovir Disoproxil Fumarate:* There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations following the administration of VIREAD.

**Gender**

*Emtricitabine and Tenofovir Disoproxil Fumarate:* Emtricitabine and tenofovir pharmacokinetics are similar in male and female subjects.

**Pediatric Patients**

The pharmacokinetic data for tenofovir and emtricitabine following administration of TRUVADA in pediatric subjects weighing 17 kg and above are not available. The dosing recommendations of TRUVADA in this population are based on the dosing recommendations of EMTRIVA and VIREAD in this population. Refer to the EMTRIVA and VIREAD prescribing information for pharmacokinetic information on the individual products in pediatric patients.
TRUVADA should not be administered to HIV-1 infected pediatric patients weighing less than 17 kg.

Geriatric Patients

Pharmacokinetics of emtricitabine and tenofovir have not been fully evaluated in the elderly (65 years of age and older).

Patients with Impaired Renal Function

The pharmacokinetics of emtricitabine and tenofovir are altered in subjects with renal impairment [see Warnings and Precautions (5.3)]. In adult subjects with creatinine clearance below 50 mL/min, C\text{max} and AUC\text{0}\text{–}\infty of emtricitabine and tenofovir were increased. It is recommended that the dosing interval for TRUVADA be modified in HIV-infected adult patients with estimated creatinine clearance 30–49 mL/min. No data are available to make dose recommendations in pediatric patients with renal impairment. TRUVADA should not be used in patients with estimated creatinine clearance below 30 mL/min and in patients with end-stage renal disease requiring dialysis [see Dosage and Administration (2.4)].

TRUVADA for a PrEP indication should not be used in HIV-1 uninfected individuals with estimated creatinine clearance below 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use [see Dosage and Administration (2.4)].

Patients with Hepatic Impairment

The pharmacokinetics of tenofovir following a 300 mg dose of VIREAD have been studied in non-HIV infected subjects with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in subjects with hepatic impairment compared with unimpaired subjects. The pharmacokinetics of TRUVADA or emtricitabine have not been studied in subjects with hepatic impairment; however, emtricitabine is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Assessment of Drug Interactions

The steady state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil fumarate were administered together versus each agent dosed alone.

In vitro studies and clinical pharmacokinetic drug-drug interaction trials have shown that the potential for CYP mediated interactions involving emtricitabine and tenofovir with other medicinal products is low.

No clinically significant drug interactions have been observed between emtricitabine and famciclovir, indinavir, stavudine, tenofovir disoproxil fumarate, and zidovudine (see Tables 8 and 9). Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and efavirenz, methadone, nelfinavir, oral contraceptives, ribavirin, or sofosbuvir in trials conducted in healthy volunteers (see Tables 10 and 11).
<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug (mg)</th>
<th>Emtricitabine Dose (mg)</th>
<th>N</th>
<th>% Change of Emtricitabine Pharmacokinetic Parameters (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Tenofvir DF</td>
<td>300 once daily × 7 days</td>
<td>200 once daily × 7 days</td>
<td>17</td>
<td>⇐</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>300 twice daily × 7 days</td>
<td>200 once daily × 7 days</td>
<td>27</td>
<td>⇐</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 × 1</td>
<td>200 × 1</td>
<td>12</td>
<td>⇐</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500 × 1</td>
<td>200 × 1</td>
<td>12</td>
<td>⇐</td>
</tr>
<tr>
<td>Stavudine</td>
<td>40 × 1</td>
<td>200 × 1</td>
<td>6</td>
<td>⇐</td>
</tr>
</tbody>
</table>

a. All interaction trials conducted in healthy volunteers

b. ↑ = Increase; ↓ = Decrease; ⇐ = No Effect; NA = Not Applicable
Table 9  Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Emtricitabine<sup>a</sup>

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug (mg)</th>
<th>Emtricitabine Dose (mg)</th>
<th>N</th>
<th>% Change of Coadministered Drug Pharmacokinetic Parameters (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 once daily × 7 days</td>
<td>200 once daily × 7 days</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td></td>
<td></td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>300 twice daily × 7 days</td>
<td>200 once daily × 7 days</td>
<td>27</td>
<td>↑ 17 (↑ 0 to ↑ 38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ 13 (↑ 5 to ↑ 20)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 × 1</td>
<td>200 × 1</td>
<td>12</td>
<td>↔</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>500 × 1</td>
<td>200 × 1</td>
<td>12</td>
<td>↔</td>
</tr>
<tr>
<td>Stavudine</td>
<td>40 × 1</td>
<td>200 × 1</td>
<td>6</td>
<td>↔</td>
</tr>
</tbody>
</table>

<sup>a</sup> All interaction trials conducted in healthy volunteers

b. ↑ = Increase; ↓ = Decrease; ↔ = No Effect; NA = Not Applicable
Table 10 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir\(^a\) in the Presence of the Coadministered Drug

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug (mg)</th>
<th>N</th>
<th>% Change of Tenofovir Pharmacokinetic Parameters(^b) (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(C_{\text{max}})</td>
</tr>
<tr>
<td>Atazanavir(^c)</td>
<td>400 once daily (\times) 14 days</td>
<td>33</td>
<td>↑ 14 ((\uparrow 8 \text{ to } \uparrow 20))</td>
</tr>
<tr>
<td>Atazanavir/ Ritonavir(^c)</td>
<td>300/100 once daily</td>
<td>12</td>
<td>↑ 34 ((\uparrow 20 \text{ to } \uparrow 51))</td>
</tr>
<tr>
<td>Darunavir/ Ritonavir(^d)</td>
<td>300/100 twice daily</td>
<td>12</td>
<td>↑ 24 ((\uparrow 8 \text{ to } \uparrow 42))</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 three times daily (\times) 7 days</td>
<td>13</td>
<td>↑ 14 ((\downarrow 3 \text{ to } \uparrow 33))</td>
</tr>
<tr>
<td>Ledipasvir/ Sofosbuvir(^e,f)</td>
<td>90/400 once daily (\times) 10 days</td>
<td>24</td>
<td>↑ 47 ((\uparrow 37 \text{ to } \uparrow 58))</td>
</tr>
<tr>
<td>Ledipasvir/ Sofosbuvir(^e,g)</td>
<td>90/400 once daily (\times) 14 days</td>
<td>15</td>
<td>↑ 79 ((\uparrow 56 \text{ to } \uparrow 104))</td>
</tr>
<tr>
<td>Ledipasvir/ Sofosbuvir(^h)</td>
<td>90/400 once daily (\times) 10 days</td>
<td>14</td>
<td>↑ 32 ((\uparrow 25 \text{ to } \uparrow 39))</td>
</tr>
<tr>
<td>Lopinavir/ Ritonavir</td>
<td>400/100 twice daily (\times) 14 days</td>
<td>24</td>
<td>⇐</td>
</tr>
<tr>
<td>Saquinavir/ Ritonavir</td>
<td>1000/100 twice daily (\times) 14 days</td>
<td>35</td>
<td>⇐</td>
</tr>
<tr>
<td>Sofosbuvir(^i)</td>
<td>400 single dose</td>
<td>16</td>
<td>↑ 25 ((\uparrow 8 \text{ to } \uparrow 45))</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.05 mg/kg twice daily (\times) 7 days</td>
<td>21</td>
<td>↑ 13 ((\uparrow 1 \text{ to } \uparrow 27))</td>
</tr>
<tr>
<td>Tipranavir/ Ritonavir(^k)</td>
<td>500/100 twice daily</td>
<td>22</td>
<td>↓ 23 ((\downarrow 32 \text{ to } \downarrow 13))</td>
</tr>
<tr>
<td></td>
<td>750/200 twice daily (23 \text{ doses})</td>
<td>20</td>
<td>↓ 38 ((\downarrow 46 \text{ to } \downarrow 29))</td>
</tr>
</tbody>
</table>
Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016

a. Subjects received VIREAD 300 mg once daily
b. Increase = ↑; Decrease = ↓; No Effect = ↔; NC = Not Calculated
c. Reyataz Prescribing Information
d. Prezista Prescribing Information
e. Data generated from simultaneous dosing with HARVONI (ledipasvir/sofosbuvir). Staggered administration (12 hours apart) provided similar results.
f. Comparison based on exposures when administered as atazanavir/ritonavir + emtricitabine/tenofovir DF.
g. Comparison based on exposures when administered as darunavir/ritonavir + emtricitabine/tenofovir DF.
h. Study conducted with ATRIPLA (efavirenz/emtricitabine/tenofovir DF) coadministered with HARVONI.
i. Study conducted with COMPLERA (emtricitabine/rilpivirine/tenofovir DF) coadministered with HARVONI.
j. Study conducted with ATRIPLA coadministered with SOVALDI® (sofosbuvir).
k. Aptivus Prescribing Information.

No effect on the pharmacokinetic parameters of the following coadministered drugs was observed with TRUVADA: abacavir, didanosine (buffered tablets), emtricitabine, entecavir and lamivudine.
<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug (mg)</th>
<th>N</th>
<th>% Change of Coadministered Drug Pharmacokinetic Parameters a (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Abacavir</td>
<td>300 once</td>
<td>8</td>
<td>↑ 12 (↓ 1 to ↑ 26)</td>
</tr>
<tr>
<td>Atazanavir&lt;sup&gt;b&lt;/sup&gt;</td>
<td>400 once daily × 14 days</td>
<td>34</td>
<td>↓ 21 (↓ 27 to ↓ 14)</td>
</tr>
<tr>
<td>Atazanavir&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Atazanavir/Ritonavir 300/100 once daily × 42 days</td>
<td>10</td>
<td>↓ 28 (↓ 50 to ↑ 5)</td>
</tr>
<tr>
<td>Darunavir&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Darunavir/Ritonavir 300/100 once daily</td>
<td>12</td>
<td>↑ 16 (↓ 6 to ↑ 42)</td>
</tr>
<tr>
<td>Didanosine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>250 once, simultaneously with tenofovir DF and a light meal&lt;sup&gt;f&lt;/sup&gt;</td>
<td>33</td>
<td>↓ 20 (↓ 32 to ↓ 7)</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 once daily × 7 days</td>
<td>17</td>
<td>⇐</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 three times daily × 7 days</td>
<td>12</td>
<td>↓ 11 (↓ 30 to ↑ 12)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>1 once daily x 10 days</td>
<td>28</td>
<td>⇐</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>150 twice daily × 7 days</td>
<td>15</td>
<td>↓ 24 (↓ 34 to ↓ 12)</td>
</tr>
<tr>
<td>Lopinavir Ritonavir</td>
<td>Lopinavir/Ritonavir 400/100 twice daily × 14 days</td>
<td>24</td>
<td>⇐</td>
</tr>
<tr>
<td>Saquinavir Ritonavir</td>
<td>Saquinavir/Ritonavir 1000/100 twice daily × 14 days</td>
<td>32</td>
<td>↑ 22 (↑ 6 to ↑ 41)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0.05 mg/kg twice daily × 7 days</td>
<td>21</td>
<td>⇐</td>
</tr>
<tr>
<td>Tipranavir&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Tipranavir/Ritonavir 500/100 twice daily</td>
<td>22</td>
<td>↓ 17 (↓ 26 to ↓ 6)</td>
</tr>
<tr>
<td>Tipranavir&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Tipranavir/Ritonavir 750/200 twice daily (23 doses)</td>
<td>20</td>
<td>↓ 11 (↓ 16 to ↓ 4)</td>
</tr>
</tbody>
</table>
Applicati on for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016

a. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

b. Reyataz Prescribing Information

c. In HIV-infected subjects, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and Cmin values of atazanavir that were 2.3 and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

d. Prezista Prescribing Information.

e. Videx EC Prescribing Information. Subjects received didanosine enteric-coated capsules.

f. 373 kcal, 8.2 g fat

g. Compared with didanosine (enteric-coated) 400 mg administered alone under fasting conditions.

h. Increases in AUC and Cmin are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

i. Aptivus Prescribing Information.

Coadministration of tenofovir disoproxil fumarate with didanosine results in changes in the pharmacokinetics of didanosine that may be of clinical significance. Concomitant dosing of tenofovir disoproxil fumarate with didanosine enteric-coated capsules significantly increases the Cmax and AUC of didanosine. When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures of didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions. The mechanism of this interaction is unknown. See Drug Interactions (7.1) regarding use of didanosine with VIREAD.

12.4 Microbiology

Mechanism of Action

Emtricitabine: Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5’-triphosphate. Emtricitabine 5’-triphosphate inhibits the activity of the HIV-1 reverse transcriptase (RT) by competing with the natural substrate deoxycytidine 5’-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine-triphosphate5’ is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.

Tenofovir Disoproxil Fumarate: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine-triphosphate5’ and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity

Emtricitabine and Tenofovir Disoproxil Fumarate: No antagonism was observed in combination studies evaluating the cell culture antiviral activity of emtricitabine and tenofovir together.

Emtricitabine: The antiviral activity of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC50) values for emtricitabine were in the range of 0.0013−0.64 μM (0.0003–0.158 μg/mL). In drug
combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC50 values ranged from 0.007–0.075 μM) and showed strain specific activity against HIV-2 (EC50 values ranged from 0.007–1.5 μM).

**Tenofovir Disoproxil Fumarate:** The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC50 values for tenofovir were in the range of 0.04–8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), no antagonism was observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O (EC50 values ranged from 0.5–2.2 μM) and showed strain specific activity against HIV-2 (EC50 values ranged from 1.6 μM to 5.5 μM).

**Prophylactic Activity in a Nonhuman Primate Model of HIV Transmission**

**Emtricitabine and Tenofovir Disoproxil Fumarate:** The prophylactic activity of the combination of daily oral emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) was evaluated in a controlled study of macaques inoculated once weekly for 14 weeks with SIV/HIV-1 chimeric virus (SHIV) applied to the rectal surface. Of the 18 control animals, 17 became infected after a median of 2 weeks. In contrast, 4 of the 6 animals treated daily with oral FTC and TDF remained uninfected and the two infections that did occur were significantly delayed until 9 and 12 weeks and exhibited reduced viremia. An M184I-expressing FTC-resistant variant emerged in 1 of the 2 macaques after 3 weeks of continued drug exposure.

**Resistance**

**Emtricitabine and Tenofovir Disoproxil Fumarate:** HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in reduced susceptibility to tenofovir.

In a clinical trial of treatment-naïve subjects [Study 934, see Clinical Studies (14.1)], resistance analysis was performed on HIV-1 isolates from all confirmed virologic failure subjects with greater than 400 copies/mL of HIV-1 RNA at Week 144 or early discontinuation. Development of efavirenz resistance-associated substitutions occurred most frequently and was similar between the treatment arms. The M184V amino acid substitution, associated with resistance to EMTRIVA and lamivudine, was observed in 2/19 analyzed subject isolates in the EMTRIVA + VIREAD group and in 10/29 analyzed subject isolates in the zidovudine/lamivudine group. Through 144 weeks of Study 934,
no subjects have developed a detectable K65R or K70E substitution in their HIV-1 as analyzed through standard genotypic analysis.

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

**Tenofovir Disoproxil Fumarate:** HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

In treatment-naïve subjects, isolates from 8/47 (17%) analyzed subjects developed the K65R substitution in the VIREAD arm through 144 weeks; 7 occurred in the first 48 weeks of treatment and 1 at Week 96. In treatment-experienced subjects, 14/304 (5%) isolates from subjects failing VIREAD through Week 96 showed greater than 1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of the resistant isolates showed a K65R amino acid substitution in the HIV-1 RT.

**iPrEx Trial:** In a clinical study of HIV-1 seronegative subjects [iPrEx Trial, see Clinical Studies (14.2)], no amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 48 subjects in the TRUVADA group and 83 subjects in the placebo group who became infected with HIV-1 during the trial. Ten subjects were observed to be HIV-1 infected at time of enrollment. The M184V/I substitutions associated with resistance to emtricitabine were observed in 3 of the 10 subjects (2 of 2 in the TRUVADA group and 1 of 8 in the placebo group). One of the two subjects in the TRUVADA group harbored wild type virus at enrollment and developed the M184V substitution 4 weeks after enrollment. The other subject had indeterminate resistance at enrollment but was found to have the M184I substitution 4 weeks after enrollment.

**Partners PrEP Trial:** In a clinical study of HIV-1 seronegative subjects [Partners PrEP Trial, see Clinical Studies (14.3)], no variants expressing amino acid substitutions associated with resistance to emtricitabine or tenofovir were detected at the time of seroconversion among 12 subjects in the TRUVADA group, 15 subjects in the VIREAD group, and 51 subjects in the placebo group. Fourteen subjects were observed to be HIV-1 infected at the time of enrollment (3 in the TRUVADA group, 5 in the VIREAD group, and 6 in the placebo group). One of the three subjects in the TRUVADA group who was infected with wild type virus at enrollment selected an M184V expressing virus by week 12. Two of the five subjects in the VIREAD group had tenofovir-resistant viruses at the time of seroconversion; one subject infected with wild type virus at enrollment developed a K65R substitution by week 16, while the second subject had virus expressing the combination of D67N and K70R substitutions upon seroconversion at week 60, although baseline virus was not genotyped and it is unclear if the resistance emerged or was transmitted. Following enrollment, 4 subjects (2 in the VIREAD group, 1 in the TRUVADA group, and 1 in the placebo group) had virus expressing K103N or V106A substitutions, which confer high-level resistance to NNRTIs but have not been associated with tenofovir or emtricitabine and may have been present in the infecting virus.
Cross Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance among certain nucleoside reverse transcriptase inhibitors (NRTIs) has been recognized. The M184V/I and/or K65R substitutions selected in cell culture by the combination of emtricitabine and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either emtricitabine or lamivudine, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

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

Tenofovir Disoproxil Fumarate: The K65R and K70E substitutions selected by tenofovir are also selected in some HIV-1-infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R and K70E substitutions also showed reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbors the K65R or K70E substitutions. HIV-1 isolates from subjects (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V substitution without zidovudine resistance-associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4), all of whom had a reduced response.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

**Tenofovir Disoproxil Fumarate:** Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in four animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

14 CLINICAL STUDIES

Clinical Study 934 supports the use of TRUVADA tablets for the treatment of HIV-1 infection. Additional data in support of the use of TRUVADA are derived from clinical Study 903, in which lamivudine and tenofovir disoproxil fumarate (tenofovir DF) were used in combination in treatment-naïve adults, and clinical Study 303 in which emtricitabine and lamivudine demonstrated comparable efficacy, safety and resistance patterns as part of multidrug regimens. For additional information about these trials, consult the prescribing information for tenofovir DF and emtricitabine. The iPrEx study and Partners PrEP study support the use of TRUVADA to help reduce the risk of acquiring HIV-1.
14.1 Study 934

Data through 144 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter trial comparing emtricitabine + tenofovir DF administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve subjects. From Weeks 96 to 144 of the trial, subjects received TRUVADA with efavirenz in place of emtricitabine + tenofovir DF with efavirenz. Subjects had a mean age of 38 years (range 18–80), 86% were male, 59% were Caucasian and 23% were Black. The mean baseline CD4+ cell count was 245 cells/mm³ (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 log₁₀ copies/mL (range 3.56–6.54). Subjects were stratified by baseline CD4+ cell count (< or ≥200 cells/mm³); 41% had CD4+ cell counts <200 cells/mm³ and 51% of subjects had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 and 144 weeks for those subjects who did not have efavirenz resistance at baseline are presented in Table 12.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>At Week 48</th>
<th>At Week 144</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTC + TDF + EFV (N=244)</td>
<td>AZT/3TC + EFV (N=243)</td>
</tr>
<tr>
<td>Responderb</td>
<td>84%</td>
<td>73%</td>
</tr>
<tr>
<td>Virologic failurec</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Rebound</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Never suppressed</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Change in antiretroviral regimen</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Death</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Discontinued due to adverse event</td>
<td>4%</td>
<td>9%</td>
</tr>
<tr>
<td>Discontinued for other reasonsd</td>
<td>10%</td>
<td>14%</td>
</tr>
</tbody>
</table>

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.

Through Week 48, 84% and 73% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <400 copies/mL (71% and 58% through Week 144). The difference in the proportion of subjects who achieved and maintained HIV-1 RNA <400 copies/mL through 48 weeks largely results from the higher number of discontinuations due to adverse events and other reasons in the zidovudine/lamivudine group in this open-label trial. In addition, 80% and 70% of subjects in the emtricitabine + tenofovir DF group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL through Week 48 (64% and 56% through Week 144). The mean increase from baseline in CD4⁺ cell count was 190 cells/mm³ in the emtricitabine +
tenofovir DF group and 158 cells/mm³ in the zidovudine/lamivudine group at Week 48 (312 and 271 cells/mm³ at Week 144).

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

14.2 iPrEx Trial

The iPrEx trial was a randomized double-blind placebo-controlled multinational study evaluating TRUVADA 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. Evidence of high risk behavior included any one of the following reported to have occurred up to six months prior to study screening: no condom use during anal intercourse with an HIV-1 positive partner or a partner of unknown HIV status; anal intercourse with more than 3 sex partners; exchange of money, gifts, shelter or drugs for anal sex; sex with male partner and diagnosis of sexually transmitted infection; no consistent use of condoms with sex partner known to be HIV-1 positive.

All subjects received monthly HIV-1 testing, risk-reduction counseling, condoms and management of sexually transmitted infections. Of the 2,499 enrolled, 1,251 received TRUVADA and 1,248 received placebo. The mean age of subjects was 27 years, 5% were Asian, 9% Black, 18% White, and 72% Hispanic/Latino.

Subjects were followed for 4,237 person-years. The primary outcome measure for the study 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. Efficacy was therefore strongly correlated with adherence.

14.3 Partners PrEP Trial

The Partners PrEP trial was a randomized, double-blind, placebo-controlled 3-arm trial conducted in 4,758 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.

All subjects received monthly HIV-1 testing, evaluation of adherence, assessment of sexual behavior, and safety evaluations. Women who became pregnant during the trial had study drug interrupted for the duration of the pregnancy and while breastfeeding. The uninfected partner subjects were predominantly male (61–64% across study drug groups), and had a mean age of 33–34 years.
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. Efficacy was therefore strongly correlated with adherence.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRUVADA tablets are available in bottles containing 30 tablets with child-resistant closure as follows:

- 100 mg of emtricitabine and 150 mg of tenofovir disoproxil fumarate (equivalent to 123 mg of tenofovir disoproxil) tablets are blue, oval-shaped, film-coated, debossed with “GSI” on one side and “703” on the other side (NDC 61958-0703-1).
- 133 mg of emtricitabine and 200 mg of tenofovir disoproxil fumarate (equivalent to 163 mg of tenofovir disoproxil) are blue, rectangular-shaped, film-coated, debossed with “GSI” on one side and “704” on the other side (NDC 61958-0704-1).
- 167 mg of emtricitabine and 250 mg of tenofovir disoproxil fumarate (equivalent to 204 mg of tenofovir disoproxil) are blue, modified capsule shaped, film-coated, debossed with “GSI” on one side and “705” on the other side (NDC 61958-0705-1).
- 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil) are blue, capsule-shaped, film-coated, debossed with “GILEAD” on one side and “701” on the other side (NDC 61958-0701-1).

Store at 25 °C (77 °F), excursions permitted to 15 °C–30 °C (59 °F–86 °F) (see USP Controlled Room Temperature).
- Keep container tightly closed
- Dispense only in original container
- Do not use if seal over bottle opening is broken or missing

17 PATIENT COUNSELING INFORMATION

As a part of patient counseling, healthcare providers must review the TRUVADA Medication Guide with every uninfected individual taking TRUVADA to reduce the risk of acquiring HIV.

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Important Information for All Patients and Uninfected Individuals

Advise patients and uninfected individuals that:
- The long term effects of TRUVADA are unknown.
- TRUVADA tablets are for oral ingestion only.
Patients and uninfected individuals should not discontinue TRUVADA without first informing their physicians.

Patients and uninfected individuals should remain under the care of a physician when using TRUVADA.

It is important to take TRUVADA on a regular dosing schedule to avoid missing doses.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Treatment with TRUVADA should be suspended in patients or uninfected individuals who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity (including nausea, vomiting, unusual or unexpected stomach discomfort, and weakness) [see Warnings and Precautions (5.1)].

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and HIV-1 and have discontinued TRUVADA. Before initiating TRUVADA, test all patients and uninfected individuals for HBV. All patients who are infected with HBV need close medical follow-up for several months after stopping TRUVADA to monitor for exacerbations of hepatitis [see Warnings and Precautions (5.2)].

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported in association with the use of VIREAD. TRUVADA should be avoided with concurrent or recent use of a nephrotoxic agent (e.g., high-dose or multiple NSAIDs) [see Warnings and Precautions (5.3)]. Dosing interval of TRUVADA may need adjustment in HIV-1 infected patients with renal impairment. TRUVADA for a PrEP indication should not be used in HIV-1 uninfected individuals if estimated creatinine clearance is less than 60 mL/min. If a decrease in estimated creatinine clearance is observed in uninfected individuals while using TRUVADA for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use [see Dosage and Administration (2.4)].

Do not administer TRUVADA with ATRIPLA, COMPLERA, EMTRIVA, GENVOYA, ODEFSEY, STRIBILD, or VIREAD; or with drugs containing lamivudine, including Combivir (lamivudine/zidovudine), Dutrebin (lamivudine/raltegravir), Epivir or Epivir-HBV (lamivudine), Epzicom (abacavir sulfate/lamivudine), Trumeq (abacavir sulfate/dolutegravir/lamivudine), or Trizivir (abacavir sulfate/lamivudine/zidovudine) [see Warnings and Precautions (5.4)].

Do not administer TRUVADA with HEPSERA [see Warnings and Precautions (5.4)].

Decreases in bone mineral density have been observed with the use of VIREAD or TRUVADA. Consider bone monitoring in patients and uninfected individuals who have a history of pathologic bone fracture or at risk for osteopenia [see Warnings and Precautions (5.5)].

Patients and uninfected individuals should avoid doing things that can spread HIV-1 or HBV infection:

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

Patients and uninfected individuals should not breastfeed because the drugs in TRUVADA can be passed to the baby in breast milk, and it is not known whether they can harm the baby. HIV-positive women should also not breastfeed because of the risk of passing the HIV-1 virus to the baby.

**Treatment of HIV-1 Infection**

When TRUVADA is used in the treatment of HIV-infection, advise patients that:

- TRUVADA is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections.
- It is important to take TRUVADA in a regular dosing schedule with combination therapy to avoid missing doses.
- All patients with HIV-1 should be tested for hepatitis B virus (HBV) before initiating and monitored after discontinuing taking TRUVADA.

**Pre-Exposure Prophylaxis**

When TRUVADA is used to reduce the risk of acquiring HIV-1, advise uninfected individuals about the importance of the following:

- Confirming that they are HIV-negative before starting to take TRUVADA to reduce the risk of acquiring HIV-1.
- TRUVADA should only be used as part of a complete prevention strategy including other prevention measures. In clinical trials, TRUVADA only protected some subjects from acquiring HIV-1.
- Using condoms consistently and correctly to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood.
- Knowing their HIV status and the status of their partner(s).
- Getting tested regularly (at least every 3 months) for HIV-1 and ask their partner(s) to get tested as well.
- HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking TRUVADA, because TRUVADA alone does not constitute a complete regimen for HIV-1 treatment [see Warnings and Precautions (5.9)]
- Reporting any symptoms of acute HIV-1 infection (flu-like symptoms) to their healthcare provider immediately.
- Signs and symptoms of acute infection include: fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical and inguinal).
- Getting tested for other sexually transmitted infections such as syphilis and gonorrhea that may facilitate HIV-1 transmission.
• Learning about sexual risk behavior and getting support to help reduce sexual risk behavior.

• Taking TRUVADA on a regular dosing schedule and strictly adhere to the recommended dosing schedule to reduce the risk of acquiring HIV-1. Uninfected individuals who miss doses are at greater risk of acquiring HIV-1 than those who do not miss doses [see Warnings and Precautions (5.9)].

• Women who are pregnant should learn about the risks and benefits of TRUVADA to reduce the risk of acquiring HIV-1 during their pregnancy.

• Encourage use of the Agreement Form for Initiating TRUVADA for PrEP of Sexually Acquired HIV-1 Infection.
Application for inclusion of Truvada tablets in the WHO Model List of Essential Medicines, December 2016

TRUVADA® (tru-VAH-dah)
(emtricitabine and tenofovir disoproxil fumarate)

Read this Medication Guide before you start taking TRUVADA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

This Medication Guide provides information about two different ways that TRUVADA may be used (see the Medication Guide section “What is TRUVADA?” for important information about how TRUVADA may be used):
- to treat Human Immunodeficiency Virus-1 (HIV-1) infection, and
- to reduce the risk of getting HIV-1 infection in adults who are HIV-negative
HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

What is the most important information I should know about TRUVADA?
TRUVADA can cause serious side effects, including:

1. Too much lactic acid in your blood (lactic acidosis). Your body normally makes lactic acid, but too much lactic acid is a serious medical emergency. It can be treated, but it can also lead to death.

Call your healthcare provider right away if you get these symptoms:
- weakness or being more tired than usual
- unusual muscle pain
- being short of breath or fast breathing
- nausea, vomiting, and stomach-area pain
- cold or blue hands and feet
- feel dizzy or lightheaded
- fast or abnormal heartbeats

2. Severe liver problems. Severe liver problems can happen in people who take TRUVADA. In some cases these liver problems can lead to death. Your liver may become large and tender. You may develop fat in your liver when you take TRUVADA.

Call your healthcare provider right away if you get the following symptoms:
- your skin or the white part of your eyes turns yellow
- dark “tea-colored” urine
- light-colored stools
- loss of appetite for several days or longer
- nausea
- stomach-area pain

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

3. If you also have hepatitis B virus (HBV) infection and take TRUVADA, your hepatitis B may become worse if you stop taking TRUVADA.

Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking TRUVADA. For more information about side effects, see the section “What are the possible side effects of TRUVADA?” in this Medication Guide.

Other important information for people who take TRUVADA to help reduce their risk of getting HIV-1 infection: Before taking TRUVADA to reduce your risk of getting HIV-1 infection:
- You must be HIV-negative to start TRUVADA. You must get tested to ensure that you do not already have HIV
- Do not take TRUVADA to reduce the risk of getting HIV-1 unless you are confirmed to be HIV-negative.
- Many HIV-1 tests can miss HIV-1 infection in a person who has recently become infected. If you have flu-like
symptoms, you could have recently become infected with HIV-1. Tell your healthcare provider if you had a flu-like illness within the last month before starting TRUVADA or at any time while taking TRUVADA. Symptoms of new HIV-1 infection include:

- tiredness
- fever
- joint or muscle aches
- headache
- sore throat
- vomiting or diarrhea
- rash
- night sweats
- enlarged lymph nodes in the neck or groin

While you are taking TRUVADA to reduce your risk of getting HIV-1:

- Just taking TRUVADA may not keep you from getting HIV-1.
- You must use safer sex practices while you are taking TRUVADA to reduce your risk of getting HIV-1.
- You must stay HIV-negative to keep taking TRUVADA to reduce your risk of infection.
  - Know your HIV-1 status and the HIV-1 status of your partners.
  - Get tested for HIV-1 at least every 3 months or when your healthcare provider tells you.
  - Get tested for other sexually transmitted infections such as syphilis and gonorrhea. These infections make it easier for HIV-1 to infect you.
  - If you think you were exposed to HIV-1, tell your healthcare provider right away. They may want to do more tests to be sure you are still HIV-negative.
  - Get information and support to help reduce risky sexual behavior.
  - Have fewer sex partners.
  - Do not miss any doses of TRUVADA. Missing doses may increase your risk of getting HIV-1 infection.
- If you do become HIV-positive, you need more medicine than TRUVADA alone to treat HIV-1. TRUVADA by itself is not a complete treatment for HIV-1.
  - If you have HIV-1 and take only TRUVADA, over time your HIV-1 may become harder to treat.

What is TRUVADA?
TRUVADA contains the prescription medicines emtricitabine (EMTRIVA®) and tenofovir disoproxil fumarate (VIREAD®). TRUVADA is used:

- to treat HIV-1 infection when used with other HIV-1 medicines in adults and children who weigh at least 37 pounds (at least 17 kg).
- to help reduce the risk of getting HIV-1 infection when used with safer sex practices in:
  - HIV-negative men who have sex with men, who are at high risk of getting infected with HIV-1 through sex.
  - Male-female sex partners when one partner has HIV-1 infection and the other does not.

Use of TRUVADA to treat HIV-1 infection:
When used with other HIV-1 medicines to treat HIV-1 infection, TRUVADA may help:

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

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

- TRUVADA does not cure HIV-1 or AIDS. If you have HIV-1 infection, you must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.
- It is not known if TRUVADA is safe and effective in children with HIV-1 infection who weigh less than 37 pounds (less than 17 kg).

Use of TRUVADA to reduce the risk of HIV-1 infection:
When used with safer sex practices, TRUVADA may help to reduce the risk of getting HIV-1 infection:

- TRUVADA works better to reduce the risk of getting HIV-1 when the medicines are in your bloodstream before
Who should not take TRUVADA?

For people using TRUVADA to reduce the risk of getting HIV-1 infection:

TRUVADA can only help reduce your risk of getting HIV-1 before you are infected. Do not take TRUVADA to help reduce your risk of getting HIV-1 if:

- you already have HIV-1 infection. If you are HIV-positive, you need to take other medicines with TRUVADA to treat HIV-1. TRUVADA by itself is not a complete treatment for HIV-1.
- you do not know your HIV-1 infection status. You may already be HIV-positive. You need to take other HIV-1 medicines with TRUVADA to treat HIV-1.

What should I tell my healthcare provider before taking TRUVADA?

Tell your healthcare provider if you:

- have liver problems including hepatitis B virus infection
- have kidney problems or receive kidney dialysis treatment
- have bone problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if TRUVADA can harm your unborn baby.

If you are a female who is taking TRUVADA to reduce the risk of getting HIV-1 infection and you become pregnant while taking TRUVADA, talk to your healthcare provider to decide if you should keep taking TRUVADA.

Pregnancy Registry: A pregnancy registry collects information about your health and the health of your baby. There is a pregnancy registry for women who take medicines to treat or prevent HIV-1 during pregnancy. For more information about the registry and how it works, talk to your healthcare provider.

- are breastfeeding or plan to breastfeed.

You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
- Do not breastfeed if you take TRUVADA. TRUVADA can pass to your baby in your breast milk.
- Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Do not take TRUVADA if you also take any of the medicines listed below:

- medicines which also contain emtricitabine or tenofovir disoproxil fumarate, (ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD). These medicines contain one or more of the same active ingredients as TRUVADA.
- medicines which contain tenofovir alafenamide (GENVOYA® or ODEFSEY®)
- medicines which contain lamivudine (Combivir, Dutrebis, Epivir, Epivir-HBV, Epzicom, Triumeq, or Trizivir)
- adefovir (HEPSERA®)

TRUVADA may interact with other medicines. Especially tell your healthcare provider if you take:

- didanosine (Videx EC)
- atazanavir (Reyataz)
- ledipasvir with sofosbuvir (HARVONI®)
- darunavir (Prezista)
- lopinavir with ritonavir (Kaletra)

Your healthcare provider may need to check you more often or change your dose if you take any of these medicines and TRUVADA.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take TRUVADA?

- Take TRUVADA exactly as prescribed.
- Take TRUVADA by mouth, with or without food.
- Children who take TRUVADA are prescribed a lower strength tablet than adults.
  - Children should swallow the tablet whole. Tell your healthcare provider if your child cannot swallow the tablet whole, because they may need a different HIV-1 medicine.
Your healthcare provider will change the dose of TRUVADA as needed based on your child’s weight.

- TRUVADA is usually taken 1 time each day. Take TRUVADA at the same time each day to keep TRUVADA blood levels constant.
  - If you have kidney problems, your healthcare provider may tell you to take TRUVADA less often.
- Do not miss any doses of TRUVADA. Missing a dose lowers the amount of medicine in your blood.
- If you miss a dose of TRUVADA, take it as soon as you remember that day. Do not take more than 1 dose of TRUVADA in a day. Do not take 2 doses at the same time to make up for a missed dose. Call your healthcare provider or pharmacist if you are not sure what to do.
- Do not change your dose or stop taking TRUVADA without first talking with your healthcare provider. Stay under a healthcare provider’s care when taking TRUVADA.
- Refill your TRUVADA prescription before you run out of medicine.
- If you take too much TRUVADA, call your healthcare provider or go to the nearest hospital emergency room right away.
- If you take TRUVADA to treat HIV-1 infection, you need to take other HIV-1 medicines. Your healthcare provider will tell you what medicines to take and how to take them.
- If you take TRUVADA to reduce your risk of getting HIV-1:
  - you must also use other methods to reduce your risk of getting HIV-1. See the section “What should I avoid while taking TRUVADA?” in this Medication Guide.
  - Take TRUVADA every day, not just when you think you have been exposed to HIV-1.

What should I avoid while taking TRUVADA?
While taking TRUVADA, avoid doing things that increase your risk of getting HIV-1 or spreading HIV-1 to other people.

- See the section “What is the most important information I should know about TRUVADA?” at the beginning of this Medication Guide.
- Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom, to lower the chance of sexual contact with semen, vaginal fluids, or blood.
- Do not share personal items that can have blood or body fluids on them, such as toothbrushes and razor blades.
- Do not share or re-use needles or other injection equipment.
- Ask your healthcare provider if you have any questions about how to prevent getting HIV-1 or spreading HIV-1

What are the possible side effects of TRUVADA?
TRUVADA may cause serious side effects, including:

- See “What is the most important information I should know about TRUVADA?”
- New or worse kidney problems, including kidney failure. If you had kidney problems in the past or take another medicine that can cause kidney problems, your healthcare provider may do blood tests to check your kidneys before you start and while you are taking TRUVADA. Your healthcare provider may tell you to take TRUVADA less often, or to stop taking TRUVADA if you have kidney problems.
- Bone problems can happen in some people who take TRUVADA. Bone problems include bone pain, or softening or thinning of bones, which may lead to fractures. Your healthcare provider may need to do tests to check your bones.
- Changes in body fat can happen in people who take HIV-1 medicines. The exact cause and long-term health effects of these problems are not known. The changes may include:
  - increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body
  - loss of fat from the legs, arms, and face
  - Changes in your immune system (Immune Reconstitution Syndrome) can happen when an HIV-1-infected person starts taking HIV-1 medicines. Your immune system may get stronger, and can then cause you to develop inflammation in areas of your body where infections may have been hiding for a long time. This inflammation may cause you to have minor symptoms, such as fever, but inflammation can also lead to serious problems. Tell your healthcare provider right away if you start having any new symptoms after starting TRUVADA for treatment of HIV-1 infection.
The most common side effects of TRUVADA in people taking TRUVADA to treat HIV-1 infection
include:

- diarrhea
- nausea
- tiredness
- headache
- dizziness
- depression
- problems sleeping
- abnormal dreams
- rash
- headache
- decreased weight
- pain

Common side effects in people who take TRUVADA to reduce the risk of getting HIV-1 infection
include:

- stomach-area (abdomen)
- decreased weight
- pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go
away.

These are not all the possible side effects of TRUVADA. For more information, ask
your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRUVADA?

- Store TRUVADA at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep TRUVADA in its original container and keep the container tightly closed.
- Do not use TRUVADA if seal over bottle opening is broken or missing.

Keep TRUVADA and all other medicines out of reach of children.

General information about TRUVADA.

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

This Medication Guide summarizes the most important information about TRUVADA. If you would
like more information, talk with your healthcare provider. You can ask your healthcare provider or
pharmacist for information about TRUVADA that is written for health professionals. For more
information, call 1-800-445-3235 or go to www.TRUVADA.com.

What are the ingredients in TRUVADA?

Active ingredients: emtricitabine and tenofovir disoproxil fumarate.

Inactive ingredients: Croscarmellose sodium, lactose monohydrate, magnesium stearate,
microcrystalline cellulose, and pregelatinized starch (gluten free). The 200 mg/300 mg strength
tablets are coated with Opadry II Blue Y-30-10701, which contains FD&C Blue #2 aluminum
lake, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The 167 mg/250
mg, 133 mg/200 mg, and 100 mg/150 mg strength tablets are coated with Opadry II Blue, which
contains FD&C Blue #2 aluminum lake, hypromellose 2910, lactose monohydrate, titanium
dioxide, and triacetin.

Revised: April 2016