Dragon, Karen E. (CDC/NIOSH/EID)

From: Laura McHugh [Laura.McHugh@gilead.com]
Sent: Wednesday, September 26, 2007 8:47 PM
To: Dragon, Karen E. (CDC/NIOSH/EID)
Cc: Pamela Danagher
Subject: NIOSH Docket #105 for Viread
Attachments: Comments to NIOSH Docket No 105 for Tenofovir DF.pdf

GILEAD

September 26, 2007

National Institute for Occupational Safety and Health
Mailstop C-34
Robert A. Taft Lab
4676 Columbia Parkway
Cincinnati, Ohio 94226

Attention: Karen E. Dragon, Docket Office Assistant

Subject: Response to NIOSH Docket #105 To Not List Tenofovir Disoproxil Fumarate (Viread®) As A "Hazardous Drug"

Dear Ms. Dragon,

Attached please find Gilead's response to the subject docket. Please call me if you have any questions at 650.522.5609.

Sincerely,
GILEAD SCIENCES, INC.

Laura D. McHugh
Director, Environmental Health & Safety

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September 20, 2007

SUBMITTAL TO THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH) TO REQUEST THAT NIOSH NOT LIST TENOFOVIR DISOPROXIL FUMARATE (VIREAD®) AS A "HAZARDOUS DRUG"

EXECUTIVE SUMMARY

The critical importance of assuring the identification of hazardous products used in Health Care settings, and the provision of detailed guidelines for the handling of such products, is recognized. Also of importance is the need for a robust process for the identification of hazardous products, to assure the usefulness and applicability of listings of products considered hazardous. The purpose of this communication is to outline considerations regarding the proposed inclusion of tenofovir disoproxil fumarate (tenofovir DF, TDF, marketed under the tradename Viread®) in the listing of products fitting the National Institute for Occupational Safety and Health (NIOSH) criteria for hazardous drugs. For the reasons outlined within this document, Gilead Sciences, Inc. (Gilead) believes that tenofovir DF does not meet the NIOSH criteria for listing as a hazardous drug (refer to Section 1 below). With a view to assuring the accuracy and appropriateness of the final published listing of products considered hazardous, an overview of the relevant scientific data is provided here to support the conclusion that tenofovir DF does not fit the criteria for a hazardous drug.

Tenofovir DF has been proposed by NIOSH as a hazardous drug to be added to a list of hazardous drugs previously published in the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings 2004 (NIOSH Alert (2004)).

Gilead Sciences, Inc. (Gilead) does not believe that the scientific data support the listing of tenofovir DF as a hazardous drug because of the following:

- The therapeutic dose of 300 mg/day is not a "low dose" for systemic toxicity as defined by the NIOSH Alert (2004) and does not support the drug to be a "potent" or hazardous agent, which would require handling in the same manner as the anticancer cytotoxic drugs, hormones and other drugs currently listed in the NIOSH Alert (2004). We ask that NIOSH consider the basic precept of toxicology – the dose makes the poison – when proposing to list tenofovir DF.
- Tenofovir DF, as compared to other active pharmaceutical ingredients such as cytotoxic antineoplastics, has not been required by the U.S. Food and Drug Administration (the US FDA) to have any special handling precautions due to its toxicity and potency as is the case for the majority of compounds currently listed by the NIOSH Alert (2004).
- The nature of toxicity studies conducted according to US FDA and Organization for Economic Development (OECD) protocols requires that there be a dose that causes some degree of toxicity (up to 2 g/kg/day in some cases). As the studies conducted for reproductive and developmental toxicity and carcinogenicity are also endpoints of

concern for hazardous drugs under the NIOSH definition, some adverse findings were reported due to the requirements of the testing protocols. The doses that resulted in toxicity if extrapolated to equivalent human exposure would require hundreds of mg/day to grams/day occupational exposures. The doses to cause "-genic" effects (reproductive and developmental toxicity and carcinogenicity) listed by the NIOSH Alert (2004) criteria exceed 600 mg/kg/day or from 3 to 5 g/day for a human, which are unlikely to occur as occupational exposures.

- In the area of mutagenicity (another criteria for listing as a hazardous drug), the in vivo mutagenic profile for tenofovir DF is negative. The use of in vitro assays as predictive of human health endpoints for an anti-viral drug may be misleading, due its pharmacological mechanism of action.
- The Occupational Exposure Limit (OEL) of 200 $\mu g/m^3$ established internally by Gilead for this compound, using safety or uncertainty factors that are protective for worker health and according to the references cited in the NIOSH Alert (2004) significantly exceeds the OEL suggested as being "hazardous" within the NIOSH Alert (2004). A sufficient "margin of safety" (20 x) is available for tenofovir DF above the 10 $\mu g/m^3$ or less level that characterizes a potent or toxic drug.

Tenofovir DF is an anti-viral compound with a specific molecular target (HIV) that is given in film-coated tablets in combination with other anti-viral drugs. The potential for exposure to health care workers is reduced by the dosage form of the drug. Of note, NIOSH Publication No. 2004-165, entitled *Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings* reflects Conditions for Exposure in the handling of hazardous materials, with a focus on handling of liquid, powdered or lyophilized drugs where spills or inhalation may contribute to accidental exposure. With respect to solid oral dosage forms, specific concern is noted for handling of **un**coated tablets, whereas Viread® (tenofovir DF) is a coated tablet, and as such, exposure to health care workers through handling is unlikely.

The scientific data summarized within this document supports that tenofovir DF does not meet the criteria established by NIOSH for a "hazardous drug." Gilead requests that NIOSH not list this with other more significantly potent and toxic drugs in the NIOSH Alert (2004) so that adequate precautions be applied to hazards that merit appropriate concern to health care workers. The following provides further scientific evidence to support that tenofovir DF not be listed.

1. Introduction

Tenofovir disoproxil fumarate (Tenofovir DF, marketed under the tradename Viread®) has been proposed by the National Institute for Occupational Safety and Health (NIOSH) as a hazardous drug, to be added to a list of hazardous drugs previously published in the NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings 2004 (NIOSH Alert (2004).

The NIOSH criteria for defining a hazardous drug is the following (NIOSH Alert (2004):

1. Carcinogenicity
2. Teratogenicity or other developmental toxicity [††]
3. Reproductive toxicity [††]
4. Organ toxicity at low doses [††]
5. Genotoxicity [‡‡]
6. Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

[††]All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 mg/day or a dose of 1 mg/kg per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 µg/m3 after applying appropriate uncertainty factors [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al. 2002]. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers.

[‡‡]In evaluating mutagenicity for potentially hazardous drugs, responses from multiple test systems are needed before precautions can be required for handling such agents. The EPA evaluations include the type of cells affected and in vitro versus in vivo testing [51 Fed. Reg. 34006–34012 (1986)].

The following will review the clinical and non-clinical data for tenofovir DF and determine its applicability to the NIOSH definition of a "hazardous drug" described above.

2. Chemical and Physical Identification

Generic Name:	Tenofovir disoproxil fumarate
Synonym:	Tenofovir DF; TDF; bis-POC PMPA; PMPA Prodrug; GS-4331-05; 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl]methoxy]propyl]adenine fumarate
Chemical Abstract Service #:	202138-50-9
Molecular Formula:	$C_{23}H_{34}O_{14}N_5P$
Molecular Weight:	635.52
Appearance, Color:	White to off-white crystalline powder; Physical form for handling by health care workers is a

coated tablet.

3. Mechanism of Action and Dose / Lack of Systemic Toxicity at "Low Doses"

Tenofovir DF, a prodrug of tenofovir [an adenine nucleoside monophosphate (nucleotide) analog], is approved in several countries including the United States for the treatment of human immunodeficiency virus type-1 (HIV-1)-infected adult patients. The prodrug is converted to tenofovir, which is then converted to the active agent, tenofovir diphosphate. Tenofovir DF inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'triphosophate and, after incorporation into DNA, causes DNA chain termination (PDR, 2007).

Tenofovir DF has shown broad spectrum and potent antiviral activity against retroviruses (e.g., HIV-1, HIV-2) and hepadnaviruses *in vitro*. In patients receiving tenofovir DF, a significant and sustained decrease in HIV-1 RNA has been observed with no evidence of significant dose-related toxicity. With a relatively long half-life, the recommended oral dose of tenofovir DF is 300 mg (corresponding to 245 mg of tenofovir disoproxil) once daily, and is being used in combination with other antiretroviral drugs (PDR, 2007).

This clinical and toxicological profile would suggest that tenofovir DF is specific as an anti-viral agent and would not be a systemic toxicant at low doses as defined by the NIOSH Alert (2004). The clinical dose of 300 mg (greater than the 10 mg/day dose referred to in the NIOSH document) is in the range of doses for some over-the-counter non-steroidal anti-inflammatory drugs (NSAIDS), which are not considered hazardous under the NIOSH Alert (2004).

The clinical safety profile of the product is presented in the current U.S. Package Insert (PI) for Viread® (provided in Attachment 1 to this document). The most common adverse events that have occurred from clinical (human) use at the recommended therapeutic dose for 48 weeks are mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence (excessive stomach gas), as well as dizziness. In HIV-infected patients receiving 300 mg/day tenofovir DF orally for up to 48 weeks, decreases in bone mineral density at the lumbar spine and hip were noted; the clinical significance of these findings are unknown. Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of Viread® in HIV-infected adult patients. Renal impairment, including cases of Fanconi Syndrome, has been reported in association with the use of Viread® in HIV-infected adult patients. Although these effects are systemic effects, they are not described at "low doses" as defined in the NIOSH Alert (2004). It is also important to note these findings are observed in the setting of chronic use of the product in the treatment of HIV infection, whereas occupational exposure is anticipated to be infrequent.

Also reflected in the current U.S. prescribing information (Attachment 1) is cautionary information included in the labeling across the class of nucleoside reverse transcriptase inhibitors, including the potential for lactic acidosis, immune reconstitution syndrome, and redistribution of body fat. In addition, cautionary language regarding the potential

for exacerbation of Hepatitis B infection following cessation of treatment with Viread® is included in the labeling given the antiviral activity of tenofovir DF on the Hepatitis B virus.

The animal toxicology data also supports the conclusion that it is not a "potent" drug which causes effects at "low doses." Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs, and monkeys at exposures (based on area under the curve or AUC) 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 4 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 (refer to the prescribing information given in Attachment 1). Therefore, the animal data shows that levels must exceed human clinical doses (which are already relatively moderate to high) to cause effects and that these effects are not at "low doses" as defined by the NIOSH Alert (2004).

We would ask that NIOSH consider the basic precept of toxicology – the dose makes the poison - and not list tenofovir DF based on the lower potency of this drug compared to other drugs previously listed and the spectrum and severity of effects from the moderate to high oral dose in patients taking the drug.

4. Requirements for Testing of Laboratory Animals for Critical Toxicological Endpoints

When testing tenofovir DF and other drugs for carcinogenicity and reproductive or developmental toxicity, Gilead and other Manufacturers, are obligated under current U.S. FDA and OECD harmonized protocols to have at least one dose that causes toxicity so that margins of safety may be determined for drug administration and to verify that the material is actually administered to the animals (see historical issues with Industrial Bio-Test). In some cases, dose levels are selected such that the high dose causes significant toxicity, a mid-dose causes only minimal toxicity and a low dose provides a no-effect dose (No Observed Effect Level or NOEL). It does not appear that the study designs (including dose levels or margins of safety based on exposure) of the animal toxicity studies was considered when NIOSH previously reviewed data on tenofovir DF (and considered outcomes in these studies as positive results). Thresholds of toxicity were observed in these studies and at very high doses, equivalent in humans to more than hundreds of mg/day to g/day quantities which are highly unlikely to be achieved occupationally. Given the nature of Viread® as a solid oral dosage form, the relevant consideration for occupational exposure is exposure to dust. A very dusty environment occupationally is 10 mg/m^3 (nuisance dust). If an employee breathes 10 m^3 of air in a

day, then the resulting exposure is 100 mg/day. These highly dusty environments are usually only prevalent when handling significantly large (kg) quantities of powders and is not a relvant consideration with a coated tablet, as is the case for Viread® .

4.1 Carcinogenicity

Long-term oral carcinogenicity studies of tenofovir DF 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 infection. At the high dose in female mice (600 mg/kg/day), liver adenomas were increased at exposures 16 times that in humans. A low incidence of duodenal tumors, considered likely related to high local concentrations of tenofovir DF in the gastrointestinal tract, were observed at 600 mg/kg/day in mice. (Viread Tablets MSDS) A NOEL of 300 mg/kg/day was also noted and would be considered a very high dose (equivalent to 1.5 g to 2.1 g for an average adult weighing 50 to 70 kg, respectively). In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose (Attachment 1).

Therefore tenofovir DF is not carcinogenic in rodents at doses up to 300 mg/kg/day, a dose equivalent to approximately 2 g/day for humans. There appears to be an adequate "margin of safety" for this compound to not be a potential carcinogen in the workplace based on the available data and exposure potential as a coated tablet. It does not appear that these results would support listing as a hazardous drug under the NIOSH Alert (2004) criteria.

4.2 Developmental Toxicity

In animal studies, tenofovir DF is not considered a developmental toxicant. In an embryo-fetal developmental toxicity study in rats, tenofovir DF was administered at doses of 50, 150 and 450 mg/kg/day to pregnant female rats on days 7 through 17 of gestation. There were reduced fetal body weights at the highest dose tested but no teratogenic effects observed at any dose tested. The maternal No Observed Effect Level (NOEL) was 150 mg/kg/day and the fetal development NOEL was > 450 mg/kg/day (the highest dose tested) (Attachment 1 and Pharmacology Review / FDA Approval Package for Viread® NDA).

In an embryo-fetal developmental toxicity study in rabbits, tenofovir DF was administered at doses of 30, 100 and 300 mg/kg/day to pregnant female rabbits on days 6 through 18 of gestation. As with the rat study, there were no dosage-dependent or biologically important differences in the litter or fetal incidences of any gross external, soft tissue or skeletal alterations, i.e., it was not teratogenic. The maternal NOEL was 100 mg/kg/day (at 300 mg/kg/day there were clinical observations and decreased maternal body weight gain and feed consumption) and the fetal development NOEL was > 300 mg/kg/day (the highest dose tested (Attachment 1 and Pharmacology Review / FDA Approval Package for Viread® NDA).

It is important to note that, based on review by the US FDA, tenofovir DF is listed as Pregnancy Category B (a lower risk category than most listed agents).

These studies support that tenofovir DF is not a developmental toxicant and does not meet the criteria for a hazardous drug as described in the NIOSH Alert (2004).

4.3 Reproductive Toxicity

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF 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 (see discussion above about having a dose that causes "some" toxicity) (PDR, 2007). The reproductive NOEL was 300 mg/kg/day as at 600 mg/kg/day, female rats had an altered estrous cycle with no effect on mating or fertility (Attachment 1 and SBA).

As with the carcinogenicity data above, Gilead was obligated to have a dose with toxicity but the doses which cause reproductive toxicity are relatively high and do not meet the criteria in the NIOSH Alert (2004).

4.4 Mutagenicity

Tenofovir DF 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 (Attachment 1).

Interpretation from a hazard standpoint may result in a determination that these results are either negative (due to the negative in vivo micronucleus test) or equivocal (because of both negative and positive findings). At best, they support the footnote in the NIOSH Alert (2004) that requires that the interpretation be greater for in vivo studies. It is also possible that the pharmacological mechanism of action as a chain terminator may affect cellular mechanisms that are atypical of other drugs or chemicals tested in such assays.

The overall data do not support a mutagenic profile of this compound as compared to other compounds previously listed in the NIOSH Alert (2004).

5. Pharmacokinetics

When considering an occupational exposure for a drug given orally, the relative bioavailability by that route compared to inhalation bioavailability must be considered. The clinical pharmacokinetics of tenofovir DF has been evaluated in HIV-infected patients and in healthy volunteers following single and multiple doses of the drug. The oral bioavailability of tenofovir from Viread is approximately 25%. Pharmacokinetics are dose proportional from 75 to 600 mg. Following IV administration of tenofovir DF,

approximately 70 – 80% of the dose was recovered in the urine as unchanged tenofovir within 72 hours of dosing (Attachment 1).

In various metabolism studies in vitro, tenofovir DF is rapidly converted to tenofovir, and tenofovir is converted to the active agent, tenofovir diphosphate. Neither tenofovir DF nor tenofovir appears to interact with the cytochrome P-450-related drug metabolizing enzymes. Other than the intracellular phosphorylated species, tenofovir is not metabolized further and is excreted unchanged in the urine (Attachment 1).

The pharmacokinetics of tenofovir DF by the inhalation route of exposure, the route by which workers are most likely to be exposed, has not been studied. This is not unusual for drugs that are not intended for delivery by the inhalation route of administration. For the purposes of setting safe or acceptable limits, it is assumed that inhaled tenofovir DF is completely absorbed. The data above suggest that inhalation bioavailability could be 4 times as much as oral bioavailability.

6. Occupational Exposure Limit

The traditional approach for determining acceptable exposure limits, such as an OEL, is to identify a NOEL from animal or human studies and then to apply appropriate uncertainty, or safety factors, as necessary (Lehman and Fitzhugh, 1954; Sargent and Kirk, 1988; Galer et al., 1992; Naumann and Weideman, 1995, Baird et al., 1996; Dourson et al., 1996). The typical equation used for determining an OEL by this approach is:

$$OEL = [(NOEL)\ (BW)] / [(SF)_n\ (BR)]$$

where:

NOEL = no-observed-effect-level for the most sensitive adverse effect;

BW = body weight of an adult worker, typically assumed by default to be 70 kg;

$(SF)_n$ = a number of safety factors that considers such uncertainties as animal-to-human variability in response, human-to-human variability in response, bioavailability by different routes of exposure, biological half-life, quality of the available data, etc., and

BR = breathing rate of an adult worker, typically assumed by default to be 10 m^3/8-hour workday.

If an appropriate NOEL cannot be identified, then an appropriate lowest-observed-effect-level (LOEL) may be used. This LOEL is typically adjusted by a safety factor of up to 10 depending on the severity of the adverse effect. For instance, if the LOEL is for minor liver toxicity, the safety factor used may be 3; if the LOEL is for developmental toxicity, the safety factor used may be 10. Other issues including the quality and robustness of the

available data are considered for the determination of the magnitude of this and other safety factors.

Gilead has determined that a safe or acceptable level for tenofovir DF is 200 µg/m3 as an 8-hour time-weighted average using the above approach and as recommended in the NIOSH Alert (2004). This OEL takes into consideration the LOEL from its current therapeutic dose, application of safety factors for variability in the population and oral versus inhalation bioavailability. This OEL is greater than the 10 µg/m3 level described by the NIOSH Alert (2004).

SUMMARY AND CONCLUSION

In summary, the data on tenofovir DF support the following:

- The clinical safety profile in HIV-infected patients receiving Viread® (tenofovir DF) at the marketed dose of 300 mg once daily, as documented in the current prescribing information (Attachment 1), includes the findings listed below.

  Of note, the clinical dose of 300 mg orally once daily is considered a high but not "low dose."

  - The most common adverse events that have occurred from long-term clinical use in HIV-infected patients at the marketed dose of 300 mg once daily are mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting and flatulence (excessive stomach gas), as well as dizziness.
  - In HIV-infected patients receiving 300 mg/day tenofovir DF orally for up to 48 weeks, decreases in bone mineral density at the lumbar spine and hip were noted; the clinical significance of these findings are unknown.
  - Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of Viread® in HIV-infected adult patients.
  - Renal impairment, including cases of Fanconi Syndrome, has been reported in association with the use of Viread® in HIV-infected adult patients.

- The nonclinical safety profile of tenofovir DF includes the following:

  - There is some evidence of mutagenicity in mammalian cells but not in vivo. It was not carcinogenic in rats. In mice, only at the highest dose tested (600 mg/kg/day) was there a low incidence of tumors (liver adenomas, duodenal neoplasms).
  - Tenofovir DF is not a reproductive or developmental toxicant.

Based on review of the available data, it can be concluded that that tenofovir DF does not meet any of the criteria of a hazardous drug under the NIOSH Hazard Alert (2004). As such, it is requested that Viread® be removed from the list of new agents fitting the NIOSH criteria for hazardous drugs.

References

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ATTACHMENT 1. Current Viread® US Prescribing Information

VIREAD®

(tenofovir disoproxil fumarate) Tablets

℞ Only

WARNINGS

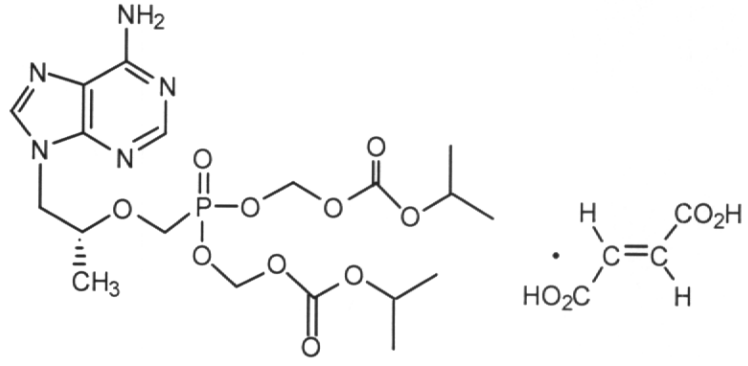
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

VIREAD IS NOT APPROVED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF VIREAD HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE COINFECTED WITH HBV AND HIV AND HAVE DISCONTINUED VIREAD. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO ARE COINFECTED WITH HIV AND HBV AND DISCONTINUE VIREAD. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

VIREAD® is the brand name for tenofovir disoproxil fumarate (a prodrug of tenofovir) which is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir disoproxil fumarate is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

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 $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25 °C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 °C.

VIREAD tablets are for oral administration. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with Opadry II Y–30–10671–A, which contains FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

In this insert, all dosages are expressed in terms of tenofovir disoproxil fumarate except where otherwise noted.

MICROBIOLOGY

Mechanism of Action: 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 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate 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: 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 EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 μM to 8.5 μM. In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 μM to 2.2 μM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 μM to 4.9 μM).

Resistance: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2–4 fold reduction in susceptibility to tenofovir.

In Study 903 of treatment-naïve patients (VIREAD + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz), genotypic analyses of isolates from patients with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated mutations to occur most frequently and with no difference between the treatment arms. The K65R mutation occurred in 8/47 (17%) analyzed patient isolates on the VIREAD arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 patients whose virus developed K65R in the VIREAD arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other mutations resulting in resistance to VIREAD were not identified in this study.

In Study 934 of treatment-naïve patients (VIREAD + EMTRIVA® + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz), genotypic analysis performed on

HIV isolates from all patients with >400 copies/mL of HIV-1 RNA at Week 48 or early discontinuation showed development of efavirenz resistance-associated mutations occurred most frequently and was similar between the two treatment arms. The M184V mutation, associated with resistance to EMTRIVA and lamivudine, was observed in 2/12 (17%) analyzed patient isolates in the VIREAD + EMTRIVA group and in 7/22 (32%) analyzed patient isolates in the zidovudine/lamivudine group. Through 48 weeks of Study 934, no patients have developed a detectable K65R mutation in their HIV as analyzed through standard genotypic analysis. Insufficient data are available to assess the development of the K65R mutation upon prolonged exposure to this regimen.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced patients (VIREAD + Standard Background Therapy (SBT) compared to Placebo + SBT), 14/304 (5%) of the VIREAD-treated patients with virologic failure through Week 96 had >1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R mutation in the HIV-1 reverse transcriptase gene.

The virologic response to VIREAD therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment experienced patients participating in Studies 902 and 907.

In these clinical studies, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI mutation. These included resistance mutations associated with zidovudine (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), the abacavir/emtricitabine/lamivudine resistance-associated mutation (M184V), and others. In addition the majority of participants evaluated had mutations associated with either PI or NNRTI use. Virologic responses for patients in the genotype substudy were similar to the overall study results.

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of VIREAD to pre-existing zidovudine resistance-associated mutations were observed and appeared to depend on the number of specific mutations. VIREAD-treated patients whose HIV-1 expressed 3 or more zidovudine resistance-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to VIREAD therapy; however, these responses were still improved compared with placebo.

The presence of the D67N, K70R, T215Y/F, or K219Q/E/N mutation did not appear to affect responses to VIREAD therapy.

In the protocol defined analyses, virologic response to VIREAD was not reduced in patients with HIV-1 that expressed the abacavir/emtricitabine/lamivudine resistance-associated M184V mutation. In the presence of zidovudine resistance-associated mutations, the M184V mutation did not affect the mean HIV-1 RNA responses to VIREAD treatment. HIV-1 RNA responses among these patients were durable through Week 48.

Studies 902 and 907 Phenotypic Analyses: The virologic response to VIREAD therapy has been evaluated with respect to baseline phenotype (N=100) in treatment-experienced patients participating in two controlled trials. Phenotypic analysis of baseline HIV-1 from patients in these studies demonstrated a correlation between baseline susceptibility to VIREAD and response to VIREAD therapy. Table 1 summarizes the HIV-1 RNA response by baseline VIREAD susceptibility.

Table 1 HIV-1 RNA Response at Week 24 by Baseline VIREAD Susceptibility (Intent-To-Treat)[1]

Baseline VIREAD Susceptibility[2]	Change in HIV-1 RNA[3] (N)
<1	-0.74 (35)
>1 and ≤3	-0.56 (49)
>3 and ≤4	-0.3 (7)
>4	-0.12 (9)

1. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).
2. Fold change in susceptibility from wild-type.
3. Average HIV-1 RNA change from baseline through Week 24 ($DAVG_{24}$) in log_{10} copies/mL.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption: VIREAD is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from VIREAD in fasted patients is approximately 25%. Following oral administration of a single dose of VIREAD 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. C_{max} and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng·hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a VIREAD dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of Food on Oral Absorption: Administration of VIREAD following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of VIREAD with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ±

119 ng/mL and 3324 ± 1370 ng·hr/mL following multiple doses of VIREAD 300 mg once daily in the fed state, when meal content was not controlled.

Distribution: In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 μg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination: In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of VIREAD, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of VIREAD 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Tenofovir pharmacokinetics are similar in male and female patients.

Pharmacokinetic studies have not been performed in children (<18 years) or in the elderly (>65 years).

The pharmacokinetics of tenofovir following a 300 mg single dose of VIREAD have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in VIREAD dosing is required in patients with hepatic impairment.

The pharmacokinetics of tenofovir are altered in patients with renal impairment **(see WARNINGS, Renal Impairment)**. In patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased (Table 2). It is recommended that the dosing interval for VIREAD be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis **(see DOSAGE AND ADMINISTRATION)**.

Table 2 Pharmacokinetic Parameters (Mean ± SD) of Tenofovir* in Patients with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	>80 (N=3)	50–80 (N=10)	30–49 (N=8)	12–29 (N=11)
C_{max} (ng/mL)	335.4 ± 31.8	330.4 ± 61.0	372.1 ± 156.1	601.6 ± 185.3
$AUC_{0-\infty}$ (ng•hr/mL)	2184.5 ± 257.4	3063.8 ± 927.0	6008.5 ± 2504.7	15984.7 ± 7223.0
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

*300 mg, single dose of VIREAD

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.

Drug Interactions

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low **(see Pharmacokinetics)**.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Coadministration of VIREAD with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the coadministered drug, due to competition for this elimination pathway. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

VIREAD has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, and saquinavir/ritonavir. Tables 3 and 4 summarize pharmacokinetic effects of coadministered drug on tenofovir pharmacokinetics and effects of VIREAD on the pharmacokinetics of coadministered drug.

Table 5 summarizes the drug interaction between VIREAD and didanosine. When administered with multiple doses of VIREAD, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown. When didanosine 250 mg enteric-coated capsules were administered with VIREAD, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Table 3 Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Adefovir dipivoxil	10 once	22	⇔	⇔	NC
Atazanavir[3]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily × 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily × 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1250 twice daily × 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)

1. Patients received VIREAD 300 mg once daily.
2. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
3. Reyataz Prescribing Information

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and VIREAD.

Table 4 Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of VIREAD

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Coadministered Drug Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑ 12 (↓ 1 to ↑ 26)	⇔	NA
Adefovir dipivoxil	10 once	22	⇔	⇔	NA
Atazanavir[2]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[2]	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[3] (↓ 42 to ↓ 3)	↓ 23[3] (↓ 46 to ↑ 10)
Efavirenz	600 once daily × 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily × 7 days	12	↓ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir	Lopinavir/Ritonavir 400/100 twice daily × 14 days	24	⇔	⇔	⇔
Ritonavir			⇔	⇔	⇔
Methadone[4]	40–110 once daily × 14 days[5]	13	⇔	⇔	⇔
Nelfinavir	1250 twice daily × 14 days	29	⇔	⇔	⇔
M8 metabolite			⇔	⇔	⇔
Oral Contraceptives[6]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily × 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Saquinavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41)	↑ 29[7] (↑ 12 to ↑ 48)	↑ 47[7] (↑ 23 to ↑ 76)
Ritonavir			⇔	⇔	↑ 23 (↑ 3 to ↑ 46)

1. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable
2. Reyataz Prescribing Information
3. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg, resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.
4. R-(active), S- and total methadone exposures were equivalent when dosed alone or with VIREAD.
5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations (opiate toxicity or withdrawal signs or symptoms) were reported.
6. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were equivalent when dosed alone or with VIREAD.
7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Table 5 Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of VIREAD

Didanosine[1] Dose (mg)/ Method of Administration[2]	VIREAD Method of Administration[2]	N	% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]	
			C_{max}	AUC
Buffered tablets				
400 once daily[4] × 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hours after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	With food, 2 hours after didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

1. See PRECAUTIONS regarding use of didanosine with VIREAD.
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. Increase = ↑; Decrease = ↓; No Effect = ⇔
4. Includes 4 subjects weighing <60 kg receiving ddI 250 mg.

INDICATIONS AND USAGE

VIREAD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Additional important information regarding the use of VIREAD for the treatment of HIV-1 infection:

- VIREAD should not be used in combination with TRUVADA® or ATRIPLA™.

Description of Clinical Studies

Treatment-Naïve Patients

Study 903: VIREAD + Lamivudine +Efavirenz Compared to Stavudine + Lamivudine + Efavirenz

Data through 144 weeks are reported for Study 903, a double-blind, active-controlled multicenter study comparing VIREAD (300 mg QD) administered in combination with lamivudine and efavirenz versus stavudine (d4T), lamivudine, and efavirenz in 600 antiretroviral-naïve patients. Patients had a mean age of 36 years (range 18–64), 74% were male, 64% were Caucasian and 20% were Black. The mean baseline CD4 cell count was 279 cells/mm^3 (range 3–956) and median baseline plasma HIV-1 RNA was 77,600 copies/mL (range 417–5,130,000). Patients were stratified by baseline HIV-1 RNA and CD4 count. Forty-three percent of patients had baseline viral loads >100,000 copies/mL and 39% had CD4 cell

counts <200 cells/mm^3. Treatment outcomes through 144 weeks are presented in Table 6.

Table 6 Outcomes of Randomized Treatment (Study 903)

Outcomes	At Week 48		At Week 144	
	VIREAD + 3TC + EFV (N=299)	d4T + 3TC + EFV (N=301)	VIREAD + 3TC + EFV (N=299)	d4T + 3TC + EFV (N=301)
	%	%	%	%
Responder[1]	79%	82%	68%	62%
Virologic failure[2]	6%	4%	10%	8%
Rebound	5%	3%	8%	7%
Never suppressed	0%	1%	0%	0%
Added an antiretroviral agent	1%	1%	2%	1%
Death	<1%	1%	<1%	2%
Discontinued due to adverse event	6%	6%	8%	13%
Discontinued for other reasons[3]	8%	7%	14%	15%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48 and 144.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48 and 144.
3. Includes lost to follow-up, patient's withdrawal, noncompliance, protocol violation and other reasons.

Achievement of plasma HIV-1 RNA concentrations of less than 400 copies/mL at Week 144 was similar between the two treatment groups for the population stratified at baseline on the basis of HIV-1 RNA concentration (> or ≤100,000 copies/mL) and CD4 cell count (< or ≥200 cells/mm^3). Through 144 weeks of therapy, 62% and 58% of patients in the VIREAD and stavudine arms, respectively achieved and maintained confirmed HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 cell count was 263 cells/mm^3 for the VIREAD arm and 283 cells/mm^3 for the stavudine arm.

Through 144 weeks, eleven patients in the VIREAD group and nine patients in the stavudine group experienced a new CDC Class C event.

Study 934: VIREAD + EMTRIVA + Efavirenz Compared with Zidovudine/Lamivudine + Efavirenz

Data through 48 weeks are reported for Study 934, a randomized, open-label, active-controlled multicenter study comparing VIREAD + EMTRIVA administered in combination with efavirenz versus zidovudine/lamivudine fixed-dose combination administered in combination with efavirenz in 511 antiretroviral-naïve patients. Patients 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/mm^3 (range 2–1191) and median baseline plasma HIV-1 RNA was 5.01 $\log_{10}$ copies/mL (range 3.56–6.54). Patients were stratified by baseline CD4 count (< or ≥200 cells/mm^3); 41% had CD4 cell counts <200 cells/mm^3 and 51% of

patients had baseline viral loads >100,000 copies/mL. Treatment outcomes through 48 weeks for those patients who did not have efavirenz resistance at baseline are presented in Table 7.

Table 7 Outcomes of Randomized Treatment at Week 48 (Study 934)

Outcome at Week 48	VIREAD + FTC + EFV (N=244)	AZT/3TC + EFV (N=243)
	%	%
Responder[1]	84%	73%
Virologic failure[2]	2%	4%
Rebound	1%	3%
Never suppressed	0%	0%
Change in antiretroviral regimen	1%	1%
Death	<1%	1%
Discontinued due to adverse event	4%	9%
Discontinued for other reasons[3]	10%	14%

1. Patients achieved and maintained confirmed HIV-1 RNA <400 copies/mL through Week 48.
2. Includes confirmed viral rebound and failure to achieve confirmed <400 copies/mL through Week 48.
3. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

The difference in the proportion of patients 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 study. In addition, 80% and 70% of patients in the VIREAD + EMTRIVA group and the zidovudine/lamivudine group, respectively, achieved and maintained HIV-1 RNA <50 copies/mL. The mean increase from baseline in CD4 cell count was 190 cells/mm^3 in the VIREAD + EMTRIVA group and 158 cells/mm^3 in the zidovudine/lamivudine group.

Through 48 weeks, 7 patients in the VIREAD + EMTRIVA group and 5 patients in the zidovudine/lamivudine group experienced a new CDC Class C event.

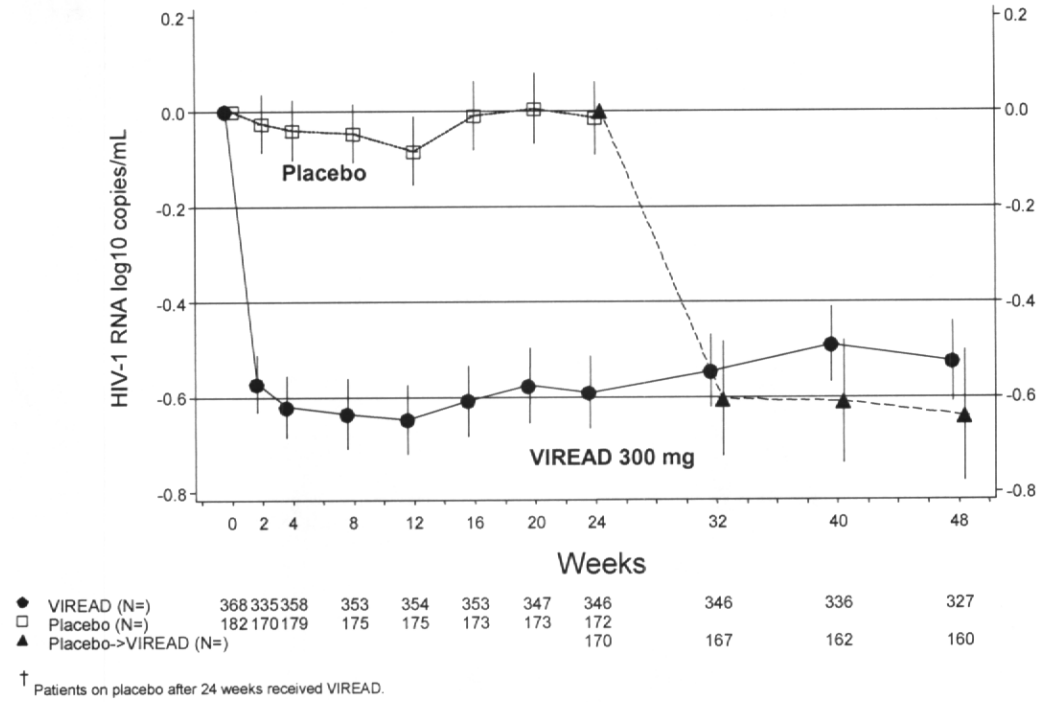
Treatment-Experienced Patients

Study 907: VIREAD + Standard Background Therapy (SBT) Compared to Placebo + SBT

Study 907 was a 24-week, double-blind placebo-controlled multicenter study of VIREAD added to a stable background regimen of antiretroviral agents in 550 treatment-experienced patients. After 24 weeks of blinded study treatment, all patients continuing on study were offered open-label VIREAD for an additional 24 weeks. Patients had a mean baseline CD4 cell count of 427 cells/mm^3 (range 23–1385), median baseline plasma HIV-1 RNA of 2340 (range 50-75,000) copies/mL, and mean duration of prior HIV-1 treatment was 5.4 years. Mean age of the patients was 42 years, 85% were male and 69% were Caucasian, 17% Black and 12% Hispanic.

Changes from baseline in log_{10} copies/mL plasma HIV-1 RNA levels over time up to Week 48 are presented below in Figure 1.

Figure 1 **Mean Change from Baseline in Plasma HIV-1 RNA (log_{10} copies/mL) Through Week 48: Study 907 (All Available Data)†**



† Patients on placebo after 24 weeks received VIREAD.

The percent of patients with HIV-1 RNA <400 copies/mL and outcomes of patients through 48 weeks are summarized in Table 8.

Table 8 **Outcomes of Randomized Treatment (Study 907)**

Outcomes	0–24 weeks		0–48 weeks	24–48 weeks
	VIREAD (N=368) %	Placebo (N=182) %	VIREAD (N=368) %	Placebo Crossover to VIREAD (N=170) %
HIV-1 RNA <400 copies/mL[1]	40%	11%	28%	30%
Virologic failure[2]	53%	84%	61%	64%
Discontinued due to adverse event	3%	3%	5%	5%
Discontinued for other reasons[3]	3%	3%	5%	1%

1. Patients with HIV-1 RNA <400 copies/mL and no prior study drug discontinuation at Week 24 and 48 respectively.
2. Patients with HIV-1 RNA ≥400 copies/mL efficacy failure or missing HIV-1 RNA at Week 24 and 48 respectively.
3. Includes lost to follow-up, patient withdrawal, noncompliance, protocol violation and other reasons.

At 24 weeks of therapy, there was a higher proportion of patients in the VIREAD arm compared to the placebo arm with HIV-1 RNA <50 copies/mL (19% and 1%, respectively). Mean change in absolute CD4 counts by Week 24 was

+11 cells/mm^3 for the VIREAD group and -5 cells/mm^3 for the placebo group. Mean change in absolute CD4 counts by Week 48 was +4 cells/mm^3 for the VIREAD group.

Through Week 24, one patient in the VIREAD group and no patients in the placebo arm experienced a new CDC Class C event.

CONTRAINDICATIONS

VIREAD is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

WARNINGS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with VIREAD should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients Coinfected with HIV and Hepatitis B Virus

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

Renal Impairment

Tenofovir is 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 in association with the use of VIREAD **(see Adverse Reactions, Post Marketing Experience).**

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with VIREAD. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

Dosing interval adjustment of VIREAD and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min **(see DOSAGE AND ADMINISTRATION)**. No safety or efficacy data are available in patients with renal dysfunction who received VIREAD using these dosing guidelines, and so the

potential benefit of VIREAD therapy should be assessed against the potential risk of renal toxicity.

VIREAD should be avoided with concurrent or recent use of a nephrotoxic agent.

Other

VIREAD should not be used in combination with the fixed-dose combination products TRUVADA or ATRIPLA since it is a component of these products.

PRECAUTIONS

Drug Interactions

When administered with VIREAD, C_{max} and AUC of didanosine (Videx, Videx EC) administered as either the buffered or enteric-coated formulation increased significantly (see Table 5). The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with VIREAD. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, VIREAD and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with VIREAD should be under fasted conditions. **Coadministration of VIREAD and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.**

Since tenofovir is primarily eliminated by the kidneys, coadministration of VIREAD with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir.

Higher tenofovir concentrations could potentiate VIREAD-associated adverse events, including renal disorders.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and lopinavir/ritonavir and VIREAD should be monitored for VIREAD-associated adverse events. VIREAD should be discontinued in patients who develop VIREAD-associated adverse events.

VIREAD decreases the AUC and C_{min} of atazanavir. When coadministered with VIREAD, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with VIREAD.

Bone Effects

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from

baseline in BMD at the lumbar spine in patients receiving VIREAD + lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the VIREAD group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated patients vs. 21% of the stavudine-treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the VIREAD group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the VIREAD group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the VIREAD group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of VIREAD **(see Adverse Reactions, Post Marketing Experience)**.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

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 patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

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

Animal Toxicology

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 4 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 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.

Pregnancy

Pregnancy Category B:

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. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VIREAD should be used during pregnancy only if clearly needed.

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

Nursing Mothers: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving VIREAD.**

Pediatric Use

Safety and effectiveness in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of 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 patient should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trials: More than 12,000 patients have been treated with VIREAD alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in Phase I–III clinical trials and expanded access studies. A total of 1,544 patients have received VIREAD 300 mg once daily in Phase I–III clinical trials; over 11,000 patients have received VIREAD in expanded access studies.

Treatment-Naïve Patients

Study 903 - Treatment-Emergent Adverse Events: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve patients received VIREAD (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse events are summarized in Table 9.

Table 9 **Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 903 (0–144 Weeks)**

	VIREAD + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic Disorders		
Lipodystrophy[1]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy[2]	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[3]	18%	12%

1. Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.
2. Peripheral neuropathy includes peripheral neuritis and neuropathy.
3. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with VIREAD (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and stavudine treatment arms. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 10.

Table 10 **Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Patients in Study 903 (0–144 Weeks)**

	VIREAD + 3TC + EFV	d4T + 3TC + EFV
	N=299	N=301
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L) (F: >170 U/L)	5%	7%
ALT (M: >215 U/L) (F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm^3)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Events: In Study 934, 511 antiretroviral-naïve patients received either VIREAD + EMTRIVA administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table 11).

Table 11 Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 934 (0–48 Weeks)

	VIREAD + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table 12).

Table 12 Significant Laboratory Abnormalities Reported in ≥1% of Patients in Any Treatment Group in Study 934 (0–48 Weeks)

	VIREAD + FTC + EFV	AZT/3TC + EFV
	N=257	N=254
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophils (<750/mm^3)	3%	4%
Fasting Triglycerides (>750 mg/dL)	4%	2%

Treatment-Experienced Patients

Treatment-Emergent Adverse Events: The adverse reactions seen in treatment experienced patients were generally consistent with those seen in treatment naïve patients including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of moderate to severe, treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in Table 13.

Table 13 **Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 907 (0–48 Weeks)**

	VIREAD (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	VIREAD (N=368) (Week 0–48)	Placebo Crossover to VIREAD (N=170) (Week 24–48)
Body as a Whole				
Asthenia	7%	6%	11%	1%
Pain	7%	7%	12%	4%
Headache	5%	5%	8%	2%
Abdominal pain	4%	3%	7%	6%
Back pain	3%	3%	4%	2%
Chest pain	3%	1%	3%	2%
Fever	2%	2%	4%	2%
Digestive System				
Diarrhea	11%	10%	16%	11%
Nausea	8%	5%	11%	7%
Vomiting	4%	1%	7%	5%
Anorexia	3%	2%	4%	1%
Dyspepsia	3%	2%	4%	2%
Flatulence	3%	1%	4%	1%
Respiratory				
Pneumonia	2%	0%	3%	2%
Nervous System				
Depression	4%	3%	8%	4%
Insomnia	3%	2%	4%	4%
Peripheral neuropathy[1]	3%	3%	5%	2%
Dizziness	1%	3%	3%	1%
Skin and Appendage				
Rash event[2]	5%	4%	7%	1%
Sweating	3%	2%	3%	1%
Musculoskeletal				
Myalgia	3%	3%	4%	1%
Metabolic				
Weight loss	2%	1%	4%	2%

1. Peripheral neuropathy includes peripheral neuritis and neuropathy.
2. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the VIREAD and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table 14.

Table 14 Grade 3/4 Laboratory Abnormalities Reported in ≥1% of VIREAD-Treated Patients in Study 907 (0–48 Weeks)

	VIREAD (N=368) (Week 0–24)	Placebo (N=182) (Week 0–24)	VIREAD (N=368) (Week 0–48)	Placebo Crossover to VIREAD (N=170) (Week 24–48)
	(%)	(%)	(%)	(%)
Any ≥ Grade 3 Laboratory Abnormality	25%	38%	35%	34%
Triglycerides (>750 mg/dL)	8%	13%	11%	9%
Creatine Kinase (M: >990U/L) (F: >845 U/L)	7%	14%	12%	12%
Serum Amylase (>175 U/L)	6%	7%	7%	6%
Urine Glucose (≥3+)	3%	3%	3%	2%
AST (M: >180 U/L) (F: >170 U/L)	3%	3%	4%	5%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%	4%	5%
Serum Glucose (>250 U/L)	2%	4%	3%	3%
Neutrophils (<750/mm^3)	1%	1%	2%	1%

Post Marketing Experience: The following events have been identified during post-approval use of VIREAD. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting or potential causal connection to VIREAD.

IMMUNE SYSTEM DISORDERS
Allergic reaction

METABOLISM AND NUTRITION DISORDERS
Hypophosphatemia, Lactic acidosis

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS
Dyspnea

GASTROINTESTINAL DISORDERS
Abdominal pain, Increased amylase, Pancreatitis

HEPATOBILIARY DISORDERS
Increased liver enzymes, Hepatitis

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Rash

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
Myopathy, Osteomalacia (both associated with proximal renal tubulopathy)

RENAL AND URINARY DISORDERS
Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus, Polyuria, Interstitial nephritis (including acute cases).

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Asthenia

OVERDOSAGE

Limited clinical experience at doses higher than the therapeutic dose of VIREAD 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

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

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.

DOSAGE AND ADMINISTRATION

The dose of VIREAD is 300 mg once daily taken orally, without regard to food.

Dose Adjustment for Renal Impairment

Significantly increased drug exposures occurred when VIREAD was administered to patients with moderate to severe renal impairment **(see CLINICAL PHARMACOLOGY)**. Therefore, the dosing interval of VIREAD should be adjusted in patients with baseline creatinine clearance <50 mL/min using the recommendations in Table 15. These dosing interval recommendations are based on modeling of single-dose pharmacokinetic data in non-HIV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring hemodialysis. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated in patients with moderate or severe renal impairment, therefore clinical response to treatment and renal function should be closely monitored in these patients **(see WARNINGS)**.

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50–80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed for these patients **(see WARNINGS)**.

Table 15 Dosage Adjustment for Patients with Altered Creatinine Clearance

	Creatinine Clearance (mL/min)[1]			Hemodialysis Patients
	≥50	30–49	10–29	
Recommended 300 mg Dosing Interval	Every 24 hours	Every 48 hours	Twice a week	Every 7 days or after a total of approximately 12 hours of dialysis[2]

1. Calculated using ideal (lean) body weight.
2. Generally once weekly assuming three hemodialysis sessions a week of approximately 4 hours duration. VIREAD should be administered following completion of dialysis.

The pharmacokinetics of tenofovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10 mL/min; therefore, no dosing recommendation is available for these patients.

HOW SUPPLIED

VIREAD is available as tablets. Each tablet contains 300 mg of tenofovir disoproxil fumarate, which is equivalent to 245 mg of tenofovir disoproxil. The tablets are almond-shaped, light blue, film-coated, and debossed with "GILEAD" and "4331" on one side and with "300" on the other side. They are packaged as follows: Bottles of 30 tablets (NDC 61958–0401–1) containing a desiccant (silica gel canister or sachet) and closed with child-resistant closure.

Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

Do not use if seal over bottle opening is broken or missing.

Gilead Sciences, Inc.
Foster City, CA 94404

May 2007

21-356-GS-020

Patient Information

VIREAD® (VEER ee ad) Tablets

Generic Name: tenofovir disoproxil fumarate (te NOE′ fo veer dye soe PROX il FYOU-mar-ate)

Read this leaflet carefully before you start taking VIREAD. Also, read it each time you get your VIREAD prescription refilled, in case something has changed. This information does not take the place of talking with your healthcare provider when you start this medicine and at check ups. You should stay under a healthcare provider's care when taking VIREAD. Do not change or stop your medicine without first talking with your healthcare provider. Talk to your healthcare provider if you have any questions about VIREAD.

What is VIREAD and how does it work?

VIREAD is a type of medicine called an HIV-1 (human immunodeficiency virus) nucleotide analog reverse transcriptase inhibitor (NRTI). VIREAD is always used in combination with other anti-HIV medicines to treat people with HIV-1 infection. VIREAD is for adults age 18 and older.

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

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

Does VIREAD cure HIV-1 or AIDS?

VIREAD does not cure HIV-1 infection or AIDS. The long-term effects of VIREAD are not known at this time. People taking VIREAD may still get opportunistic infections or other conditions that happen with HIV-1 infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

Does VIREAD reduce the risk of passing HIV-1 to others?

VIREAD does not reduce the risk of passing HIV-1 to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

Who should not take VIREAD?

Together with your healthcare provider, you need to decide whether VIREAD is right for you.

Do not take VIREAD if

- you are allergic to VIREAD or any of its ingredients

- you are already taking TRUVADA® or ATRIPLA™ because VIREAD is one of the active ingredients in TRUVADA and ATRIPLA

What should I tell my healthcare provider before taking VIREAD?
Tell your healthcare provider

- *If you are pregnant or planning to become pregnant*: The effects of VIREAD on pregnant women or their unborn babies are not known.
- *If you are breast-feeding:* Do not breast-feed if you are taking VIREAD. Do not breast-feed if you have HIV. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby. If your baby does not already have HIV, there is a chance that the baby can get HIV through breast-feeding.
- **If you have kidney or bone problems**
- **If you have liver problems including Hepatitis B Virus infection**
- **Tell your healthcare provider about all your medical conditions**

TELL YOUR HEALTHCARE PROVIDER ABOUT ALL THE MEDICINES YOU TAKE, INCLUDING PRESCRIPTION AND NON-PRESCRIPTION MEDICINES AND DIETARY SUPPLEMENTS. ESPECIALLY TELL YOUR HEALTHCARE PROVIDER IF YOU TAKE:

- VIDEX, VIDEX EC (DIDANOSINE). VIREAD MAY INCREASE THE AMOUNT OF VIDEX IN YOUR BLOOD. YOU MAY NEED TO BE FOLLOWED MORE CAREFULLY IF YOU ARE TAKING VIDEX AND VIREAD TOGETHER. IF YOU ARE TAKING VIDEX AND VIREAD TOGETHER YOUR HEALTHCARE PROVIDER MAY NEED TO REDUCE YOUR DOSE OF VIDEX.

- REYATAZ (ATAZANAVIR SULFATE) OR KALETRA (LOPINAVIR/RITONAVIR). THESE MEDICINES MAY INCREASE THE AMOUNT OF VIREAD IN YOUR BLOOD, WHICH COULD RESULT IN MORE SIDE EFFECTS. YOU MAY NEED TO BE FOLLOWED MORE CAREFULLY IF YOU ARE TAKING VIREAD AND REYATAZ OR KALETRA TOGETHER. VIREAD MAY DECREASE THE AMOUNT OF REYATAZ IN YOUR BLOOD. IF YOU ARE TAKING VIREAD AND REYATAZ TOGETHER YOU SHOULD ALSO BE TAKING NORVIR (RITONAVIR).

IT IS A GOOD IDEA TO KEEP A COMPLETE LIST OF ALL THE MEDICINES THAT YOU TAKE. MAKE A NEW LIST WHEN MEDICINES ARE ADDED OR STOPPED. GIVE COPIES OF THIS LIST TO ALL OF YOUR HEALTHCARE PROVIDERS **EVERY** TIME YOU VISIT YOUR HEALTHCARE PROVIDER OR FILL A PRESCRIPTION.

How should I take VIREAD?

- Stay under a healthcare provider's care when taking VIREAD. Do not change your treatment or stop treatment without first talking with your healthcare provider.

- Take VIREAD exactly as your healthcare provider prescribed it. Follow the directions from your healthcare provider, exactly as written on the label. Set up a dosing schedule and follow it carefully.
- The usual dose of VIREAD is 1 tablet once a day, in combination with other anti-HIV medicines. If you have kidney problems, your healthcare provider may recommend that you take VIREAD less frequently.
- VIREAD may be taken with or without a meal.
- When your VIREAD supply starts to run low, get more from your healthcare provider or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to VIREAD and become harder to treat.
- Only take medicine that has been prescribed specifically for you. Do not give VIREAD to others or take medicine prescribed for someone else.

What should I do if I miss a dose of VIREAD?

It is important that you do not miss any doses. If you miss a dose of VIREAD, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

What happens if I take too much VIREAD?

If you suspect that you took more than the prescribed dose of VIREAD, contact your local poison control center or emergency room right away.

As with all medicines, VIREAD should be kept out of reach of children.

What should I avoid while taking VIREAD?

- Do not breast-feed. See "What should I tell my healthcare provider before taking VIREAD?"

What are the possible side effects of VIREAD?

- Clinical studies: The most common side effects of VIREAD are: diarrhea, nausea, vomiting, and flatulence (intestinal gas).
- Marketing experience: Other side effects reported since VIREAD has been marketed include: weakness, inflammation of the pancreas, low blood phosphate, dizziness, shortness of breath, and rash.
- Some patients treated with VIREAD have had kidney problems. If you have had kidney problems in the past or need to take another drug that can cause kidney problems, your healthcare provider may need to perform additional blood tests.
- Laboratory tests show changes in the bones of patients treated with VIREAD. It is not known whether long-term use of VIREAD will cause damage to your bones. If you have had bone problems in the past, your healthcare provider may need to perform additional tests or may suggest additional medication.
- Some patients taking antiviral drugs like VIREAD have developed a condition called lactic acidosis (a buildup in the blood of lactic acid, the same substance that causes your muscles to burn during heavy exercise). Symptoms of lactic acidosis include nausea, vomiting, unusual or unexpected stomach discomfort,

and weakness. If you notice these symptoms or if your medical condition changes suddenly, call your healthcare provider right away.

- Changes in body fat have been seen in some patients taking anti-HIV medicine. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the main part of your body (trunk). Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- If you have hepatitis B virus (HBV) infection, you may have a "flare-up" of hepatitis B, in which the disease suddenly returns in a worse way than before if you stop taking VIREAD. VIREAD is not approved for the treatment of Hepatitis B Virus infection.
- There have been other side effects in patients taking VIREAD. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.
- This list of side effects is **not** complete. If you have questions about side effects, ask your healthcare provider. You should report any new or continuing symptoms to your healthcare provider right away. Your healthcare provider may be able to help you manage these side effects.

How do I store VIREAD?

- Keep VIREAD and all other medications out of reach of children.
- Store VIREAD at room temperature 77 °F (25 °C). It should remain stable until the expiration date printed on the label.
- Do not keep your medicine in places that are too hot or cold.
- Do not keep medicine that is out of date or that you no longer need. If you throw any medicines away make sure that children will not find them.

General advice about prescription medicines:

TALK TO YOUR HEALTHCARE PROVIDER IF YOU HAVE ANY QUESTIONS ABOUT THIS MEDICINE OR YOUR CONDITION. MEDICINES ARE SOMETIMES PRESCRIBED FOR PURPOSES OTHER THAN THOSE LISTED IN A PATIENT INFORMATION LEAFLET. IF YOU HAVE ANY CONCERNS ABOUT THIS MEDICINE, ASK YOUR HEALTHCARE PROVIDER. YOUR HEALTHCARE PROVIDER OR PHARMACIST CAN GIVE YOU INFORMATION ABOUT THIS MEDICINE THAT WAS WRITTEN FOR HEALTH CARE PROFESSIONALS. DO NOT USE THIS MEDICINE FOR A CONDITION FOR WHICH IT WAS NOT PRESCRIBED. DO NOT SHARE THIS MEDICINE WITH OTHER PEOPLE.

DO NOT USE IF SEAL OVER BOTTLE OPENING IS BROKEN OR MISSING.

What are the ingredients of VIREAD?

Active Ingredient: tenofovir disoproxil fumarate

Inactive Ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The tablets are coated with Opadry II Y–30–10671–A, which contains FD&C blue #2 aluminum lake, hydroxypropyl methylcellulose 2910, lactose monohydrate, titanium dioxide, and triacetin.

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