CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202123Orig1s000

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 202123 **SN**: 000 **SDN:** 13 **DATE REVIEWED:** 07/15/11
Virology Reviewer: Lisa K. Naeger, Ph.D.

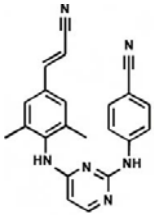
NDA#: 202,123 **Serial #:** 000
Reviewer's Name(s): Lisa K. Naeger, Ph.D.

Sponsor's Name and Address:
Gilead Sciences

Initial Submission Dates:
Correspondence Date: 02/10/11
CDER Receipt Date: 02/10/11
Assigned Date: 02/10/11
Review Complete Date: 07/15/11
PDUFA Date: 8/10/11

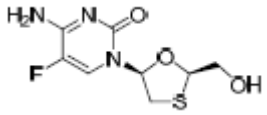
Amendments: none
Related/Supporting Documents: IND67699, NDA202022
Product Name(s)
Proprietary: *EDURANT*
Non-Proprietary/USAN: rilpivirine/truvada
Code Name/Number: TMC278/FTC/TDF

RILPIVIRINE
Chemical Name: 4-[[4-[[4-[(1*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile,
Molecular Weight: 366.42 Daltons
Molecular Formula: $C_{22}H_{18}N_6$
Structural Formula:



TMC278

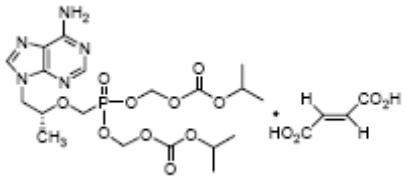
EMTRICITABINE
Chemical Name: 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine
Molecular Weight: 247.24
Molecular Formula: $C_8H_{10}FN_3O_3S$
Structural Formula:



EMTRICITABINE

TENOFOVIR DISOPROXIL FUMARATE
Chemical Name: 9-[(*R*)-2 [[bis[[(isopropoxycarbonyl)oxy]-methoxy]phosphinyl] methoxy]propyl]adenine fumarate (1:1)
Molecular Weight: 635.52

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 202123 **SN**: 000 **SDN:** 13 **DATE REVIEWED:** 07/15/11
Virology Reviewer: Lisa K. Naeger, Ph.D.
Molecular Formula: $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$
Structural Formula:



Dosage Form(s):
Route(s) of Administration: Oral
Indication(s): Treatment of HIV-1 infection in ARV treatment-naive adult patients
Dispensed: Rx X OTC_____

Abbreviations: EC_{50}, effective concentration at 50%; EFV, efavirenz; ENF, enfuvirtide; ETR, etravirine; FC, fold change; HSA, human serum albumin; IC_{50}, inhibitory concentration at 50%; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PBL, peripheral blood lymphocytes; PI, protease inhibitor; PR, protease; RAMs, resistant-associated mutations; RT, reverse transcriptase; SDM, site-directed mutants;

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Please refer to NDA202022 for complete virology review of rilpivirine in combination with emtricitabine and tenofovir DF.

NON-CLINICAL VIROLOGY

Triple Combination Studies

The triple combination of FTC + RPV + TFV was evaluated in 5-day cytopathic assays in MT-2 cells acutely infected with HIV-1. The combination effect of the three-drug combination was analyzed using the combination index method of the CalcuSyn software. For the triple drug combination studies, EC_{50} experiments were performed for each drug individually and in the triple combination, for a total of four EC_{50} experiments per experiment (Drug A alone; Drug B alone; Drug C alone; and Drug A + Drug B + Drug C).

Serial dilutions of test compounds were prepared in triplicate in 96-well plates. MT-2 cells were infected with the HIV-1_{LAI} virus at a multiplicity of infection (MOI) of 0.005 for 3 hours at 37°C. After a 5-day incubation period at 37°C, the virus-induced cytopathic effect (CPE) was determined using a cell viability assay. One hundred microliters of XTT reagent [2,3,-bis(methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide; (b) (4)) plus PMS substrate (phenazine methosulfate; (b) (4)) were added to each well with MT-2 cells. Plates were incubated at 37°C for 1 hour, and then 25 microliters of 2% Triton-X100 solution were added to each well with MT-2 cells. The plates were read on a spectrophotometer.

The triple combination of FTC + RPV + TFV showed moderate synergy, with the mean CI value of 0.73 ± 0.13. As a control for synergy, the triple combination of FTC + TFV + EFV was evaluated in parallel and yielded the expected synergy (CI = 0.57 ± 0.08)[3]. The results for these two triple combinations (FTC + RPV + TFV and FTC + TFV + EFV) were not statistically different (t-test, p=0.09). The control combination for additivity of FTC + FTC + FTC was additive (CI = 0.92 ± 0.06).

Table 1. Tabular Summary of the Triple Drug Combination Index Values

Drug Combination[a]	CI ± SD[b]	Combination Result
FTC + RPV + TFV	0.73 ± 0.13	Moderate synergy
FTC + TFV + EFV	0.57 ± 0.08	Synergy
d4T + AZT + RPV	0.92 ± 0.04	Additive
FTC + FTC + FTC	0.92 ± 0.06	Additive

a FTC, emtricitabine; RPV, rilpivirine; TFV, tenofovir ; EFV, efavirenz ; d4T, stavudine ; AZT, zidovudine.
b Mean Combination Index (CI) and standard deviation calculated from n=3-5 experiments for all combinations.

There was no evidence of antagonistic interactions among the drugs in two or three drug combinations.

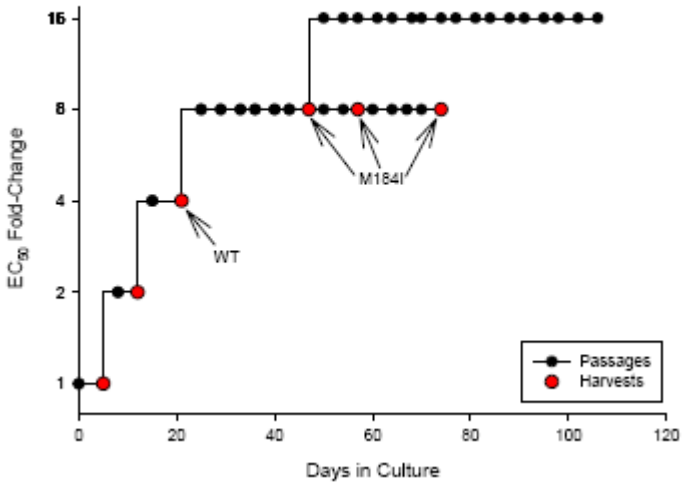
Triple Drug Resistance Selection by Emtricitabine, Rilpivirine and Tenofovir

Dose escalation (Fig. 1) and fixed-dose breakthrough selection experiments were performed using HIV strains xxLAI and IIIb, respectively. For the dose-escalation experiments, HIV-1-infected MT-2 cells were exposed to increasing concentrations of FTC + RPV + TFV in fixed ratios based on their EC_{50} values of 0.5 µM, 0.1 nM, and 3.5

µM for FTC, RPV, and TFV, respectively. The selection process was carried out for approximately 3 months.

Figure 1: Dose Escalation Selections with FTC+RPV+TFV in HIV-1 Strain xxLAI

FTC + RPV + TFV



Population sequencing of PCR-amplified cDNA generated from isolated viral RNA revealed specific mutations in the RT gene (codons 1 to 560) from viruses selected by the drug combinations. The combination of FTC + RPV + TFV resulted in HIV-1 with the M184I RT substitution by day 47, and no additional substitutions were detected at day 57 or 74.

Table. Genotypic Changes in HIV-1 Isolates Selected by Dose-escalation

Drug combination[a]	Time in culture	Concentrations reached (fold-change EC_{50})[b]	Mutation in RT gene
FTC+RPV+TFV	21 days	0.64 µM + 0.12 nM + 4.6 µM (4)	No mutations
	47 days, 57 days, 74 days	1.28 µM + 0.24 nM + 9.2 µM (8)	M184I

For the fixed-dose breakthrough experiments, HIV-1 (strain IIIb) in MT-2 cells were exposed to fixed concentrations of FTC, RPV, and TFV based on their EC_{50} values of 0.5 µM, 0.1 nM and 3.5 µM, respectively. The selection pressure of the drugs for the triple combination experiments remained at fixed 1:1:1 ratios based on the EC_{50} value for each drug. The selection process was carried out until the cultures showed extensive cytopathic effects. The combination of FTC + RPV + TFV resulted in HIV-1 with the M184I RT substitution from the 1.7x +1.7x + 1.7x EC_{50} drug culture and K65R from the 3.3x + 3.3x + 3.3x EC_{50} culture, and did not show virus replication in the higher drug concentration cultures.

Table. Genotypic Changes in HIV-1 Isolates Selected by Fixed-dose Breakthrough Selections

Drug Combination	Drug Concentration (Fold-Change EC_{50})[a]	Days to Breakthrough	Mutation in RT Gene
FTC + RPV + TFV	1.7 + 1.7 + 1.7[b]	22	M184I
	3.3 + 3.3 + 3.3	49	K65R
	6.7 + 6.7 + 6.7	—	—
	33.3 + 33.3 + 33.3	—	—

Phenotypic analyses of the final selected virus pools are currently ongoing.

Cross-Resistance

The susceptibility of FTC, TFV, and RPV to wild-type and a series of 141 mutant HIV-1 viruses containing mutations in the RT gene associated with reduced susceptibility to NRTIs and NNRTIs were determined. The panel of 141 viruses consisted of 138 viruses with NNRTI resistance-associated substitutions alone or with NRTI resistance-associated substitutions, and three viruses that only contained NRTI resistance-associated substitutions (A62V, D67N+K70R+T215F+K219Q, and M184V). The average EC_{50} values determined for FTC, TFV, and RPV against wild-type HIV-1 were 0.18 µM for FTC, 1.59 µM for TFV, and 0.49 nM for RPV. The average susceptibility change of the NNRTI mutant viruses to FTC was >5.8-fold compared to wild-type (n=136; range = 0.1- to >51.2-fold change). The major FTC resistance substitutions are M184V and M184I. The average susceptibility change of the mutant virus lacking M184V/I was 0.8-fold compared to wildtype (n=116; range 0.1- to 2.1-fold). The subset of viruses with M184V/I showed resistance with an average reduced susceptibility of >34.5-fold compared to wild-type (n=20; range >24.0- to >51.2-fold change). These data show that viruses containing NNRTI mutations that lack M184V/I are not cross-resistant to FTC.

The susceptibility of the NNRTI mutant viruses was 0.5-fold compared to wild-type (n=136; range = 0.1- to 1.2-fold change). These data show that viruses containing NNRTI substitutions are not cross-resistant to TFV.

The average susceptibility of the NNRTI mutants to RPV was 11-fold compared to wild-type (n=137; range = <0.1- to 381-fold change). The susceptibility of the NRTI-only mutant viruses expressing A62V, D67N+K70R+T215F+K219Q, and M184V substitutions to RPV were 0.9-, 0.8-, and 0.7-fold, respectively, and suggested no cross-resistance of these NRTI mutants to RPV. Overall, the results of this study demonstrate the lack of cross-resistance of HIV-1 with RPV-resistance-associated substitutions and other NNRTI resistance-associated substitutions to FTC and TFV.

CONCLUSION:

This NDA is approvable with respect to virology for the treatment of HIV-1 infection in antiretroviral treatment-naive adult patients. The **Microbiology** section of the rilpivirine label (NDA202022) has been updated to show only the Truvada subset of subjects in Studies C209 and C215.

FDA APPROVED PACKAGE INSERT

The Microbiology section of the Rilpivirine package insert was updated to include only the Truvada subset of subjects in Studies C209 and C215. Changes are shown in red.

12.4 Microbiology

Mechanism of Action

Rilpivirine: Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1) and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.

(b) (4)

[redacted]

Rilpivirine: Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1_{IIIB} of 0.73 nM (0.27 ng/mL). Rilpivirine demonstrated limited activity in cell culture against HIV-2 with a median EC_{50} value of 5220 nM (range 2510 to 10830 nM) (920 to 3970 ng/mL).

Rilpivirine demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/ml) and was less active against group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/ml).

The antiviral activity of rilpivirine was not antagonistic when combined with the NNRTIs efavirenz, etravirine or nevirapine; the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir or zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir or tipranavir; the fusion inhibitor enfuvirtide; the CCR5 co-receptor antagonist maraviroc or the integrase strand transfer inhibitor raltegravir.

(b) (4)

Resistance

In Cell Culture

(b) (4) Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI-resistant HIV-1. The frequently observed amino acid substitutions that emerged and conferred decreased susceptibility to rilpivirine included: L100I, K101E, V106I and A, V108I, E138K and G, Q, R, V179F and I, Y181C and I, V189I, G190E, H221Y, F227C and M230I and L.

(b) (4)

In Treatment-Naïve Subjects

In the pooled resistance analysis for subjects receiving rilpivirine in combination with emtricitabine/tenofovir DF in clinical trials C209 and C215 [See *Clinical Studies* (14)], the emergence of resistance was greater in the rilpivirine arms compared to the efavirenz arms (see Table 10). In the combined studies, (b) (4) of the virologic

failures in the rilpivirine arms had genotypic and phenotypic resistance to rilpivirine compared to (b) (4) of the virologic failures in the efavirenz arms who had genotypic and phenotypic resistance to efavirenz. (b) (4)

(b) (4)

Emerging NNRTI substitutions in the rilpivirine virologic failures included V90I, K101E/P/T, E138K/G, V179I/L Y181I/C, V189I, H221Y, F227C/L and M230L which were associated with a rilpivirine phenotypic fold change range of 2.6 - 621. The E138K substitution emerged most frequently on rilpivirine treatment commonly in combination with the M184I substitution. The emtricitabine and lamivudine resistance-associated substitutions M184I or V and the tenofovir resistance-associated substitutions K65R or N emerged more frequently in rilpivirine virologic failures than in efavirenz virologic failures (b) (4)

(b) (4) **Proportion of Frequently Emergent Reverse Transcriptase Substitutions in Virologic Failures from Combined Phase 3 Studies**

	C209 and C215 N=1368
	(b) (4)
Virologic Failures (As-Treated)	
Evaluable Post-Baseline Resistance Data	
	(b) (4)
V90I	(b) (4)
K101E/P/T	
K103N	
E138K/G	
*E138K + M184I	
V179I/L/D	
Y181C/I	
V189I	
H221Y	
	(b) (4)
M184I or V	(b) (4) (b) (4)
K65R/N	(b) (4) (b) (4)

*This combination of NNRTI and NRTI substitutions is a subset of those with the E138K

Cross-Resistance

(b) (4)

Cross-resistance has been observed among NNRTIs. The single NNRTI substitutions K101P, Y181I and Y181V conferred 52-fold, 15-fold and 12-fold decreased susceptibility to rilpivirine, respectively. The combination of E138K and M184I showed 6.7-fold reduced susceptibility to rilpivirine compared to 2.8-fold for E138K alone. The K103N substitution did not show reduced susceptibility to rilpivirine. Combinations of 2 or 3 NNRTI resistance-associated substitutions gave decreased susceptibility to rilpivirine (fold change range of 3.7 - 554) in 38% and 66% of mutant viruses, respectively."

Treatment-naïve HIV-1-infected subjects

Considering all of the available cell culture and clinical data, the following amino acid substitutions, when present at baseline, are likely to decrease the antiviral activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, H221Y, F227C and M230I or M230L.

Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure with a rilpivirine-containing regimen. In the pooled analyses of the Phase 3 clinical trials,

(b) (4)

were resistant to etravirine at failure. Subjects experiencing virologic failure on TRADENAME developed more NNRTI resistance-associated substitutions conferring more cross-resistance to the NNRTI class and had a higher likelihood of cross-resistance to all NNRTIs in the class than subjects who failed on EFV.

(b) (4)

7 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

LISA K NAEGER
07/11/2011

JULIAN J O'REAR
07/11/2011

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 202,123 SDN013 **Applicant: Gilead Sciences** **Stamp Date: 02/10/2011**

Drug Name: Rilpivirine/Truvada **NDA Type: Original**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X		
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			NA
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	X		
7	Has the applicant submitted the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	X		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		
9	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
11	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Lisa K. Naeger 03/08/11
Reviewing Microbiologist Date

Microbiology Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA K NAEGER
03/08/2011

JULIAN J O'REAR
03/08/2011