CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202123Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	202-123
Supporting document/s:	SN0012
Applicant's letter date:	February 10, 2011
CDER stamp date:	February 10, 2011
Product:	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate fixed dose combination tablet, 200 mg FTC/25 mg RPV/300 mg TDF
Indication:	HIV-1 infection
Applicant:	Gilead Sciences
Review Division:	Division of Antiviral Products
Reviewer:	Mark Seaton, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D., DABT
Division Director:	Debra Birnkrant, M.D.
Project Manager:	Linda C. Onaga, MPH

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202-123 are owned by Gilead or are data for which Gilead has obtained a written right of reference. Any information or data necessary for approval of NDA 202-123 that Gilead does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Gilead does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 202-123.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Gilead Science has submitted an NDA for Complera, a new combination drug product for HIV infection. The proposed fixed dose combination includes three approved drug products (emtricitabine (FTC)/rilpivirine (RPV)/tenofovir disoproxil fumarate (TDF) fixed-dose combination tablet, 200 mg FTC/25 mg RPV/300 mg TDF). All nonclinical information is cross-referenced to the original NDAs and INDs cited below and no additional nonclinical toxicology information is included in the package.

1.3 Recommendations

1.3.1 Approvability

It is recommended that Complera be approved.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

The nonclinical Pharmacology/Toxicology portion of the sponsor's drug product label is included below:

> **8.1 Pregnancy**
>
> *Pregnancy Category B*
>
> *Emtricitabine:* The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 120-times higher than human exposures at the recommended daily dose.
>
> *Rilpivirine:* Studies in animals have shown no evidence of embryonic or fetal toxicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with rilpivirine during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal No Observed Adverse Effects Levels in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily.
>
> *Tenofovir Disoproxil Fumarate:* Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Complera should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. Studies in lactating rats and their offspring indicate that rilpivirine was present in rat milk. It is not known whether emtricitabine, rilpivirine, or 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 breastfeed if they are receiving Complera.**

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Rilpivirine: Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg per kg per day were administered to mice and doses of 40, 200, 500 and 1500 mg per kg per day were administered to rats. In rats, there were no drug related neoplasms. In mice, rilpivirine was

positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21 fold (mice) and 3 fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily).

Rilpivirine has tested negative in the absence and presence of a metabolic activation system, in the in vitro Ames reverse mutation assay and in vitro clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

In a study conducted in rats, there were no effects on mating or fertility with rilpivirine up to 400 mg per kg per day, a dose of rilpivirine that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

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

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

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

13.2 Animal Toxicology and/or Pharmacology

Tenofovir Disoproxil Fumarate: 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.

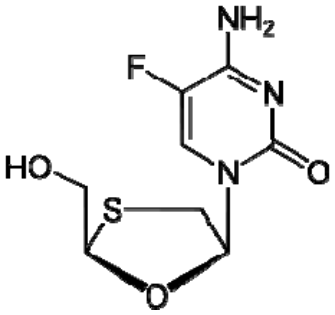
2 Drug Information

2.1 Drug

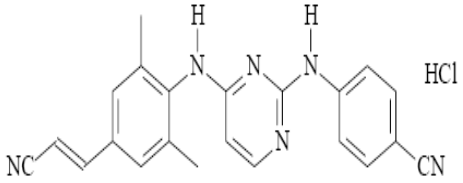
EMTRIVA (emtricitabine, FTC): CAS number 143491-57-0; chemical name 2'-deoxy-5-fluoro-3'-thiacytidine

EDURANT (rilpivirine, RPV): CAS number 700361-47-3; chemical name (E)-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile hydrochloride

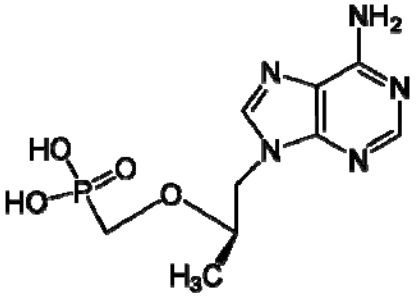
VIREAD (tenofovir disoproxil fumarate, TDF): CAS number 147127-20-6; chemical name {[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]oxy}methyl)phosphonic acid



EMTRIVA



EDURANT



VIREAD

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI). Rilpivirine is a non-nucleoside reverse transcript inhibitor (NNRTI). Tenofovir disoproxil fumarate is a nucleotide reverse transcriptase inhibitor (NtRTI).

2.2 Relevant INDs, NDAs, BLAs and DMFs

This NDA is supported by right of reference to applicable sections of Gilead NDA 21-500, NDA 21-896 and Gilead IND 53,971 for FTC, Gilead NDA 21-356 and IND 52,849 for TDF and by right of cross-reference to Tibotec NDA 202022 and IND 67,699 for RPV.

2.3 Drug Formulation

FTC/RPV/TDF tablets are (b) (4) tablets (b) (4) The tablets are capsule shaped, film-coated purplish-pink, and debossed with "GSI" on one side and plain faced on the other side.

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

The sponsor has reported higher than expected levels of degradants, specifically (b) (4) (b) (4), when FTC/RPV/TDF is stored outside of the original container and labeled storage conditions.

Based on the no observed adverse event level (NOAEL) in a 14-day rat study, taken together with results from analysis of the emtricitabine (lot no. DD-2109-2) used in that study, the (b) (4) have been qualified at levels of (b) (4) respectively for a 200 mg/day clinical dose of emtricitabine (refer to Dr. Mark Powley's Pharmacology/Toxicology Review of the sponsor's January 31, 2011 submission to NDA 21-752). In stability testing completed to date, including in stress studies with elevated temperature and relative humidity, measured levels of the (b) (4) (b) (4) have been (b) (4) the qualified levels.

Quantitative structural activity relationship evaluation of the (b) (4) indicates that the impurities possess minimal genotoxic potential.

2.6 Proposed Clinical Population and Dosing Regimen

Gilead is pursuing registration of the FTC/RPV/TDF fixed-dose combination as a complete regimen for treatment of HIV-1 infection in adults. FTC/RPV/TDF will be administered orally, once daily, with a meal.

2.7 Regulatory Background

Emtricitabine and tenofovir disoproxil fumarate have been approved for the treatment of HIV-1 infection in adults as stand-alone agents Emtriva® (NDAs 21-500 for the capsule

formulation approved on 2 July 2003 and 21-896 for an oral solution approved on 28 September 2005), Edurant® (NDA 202022 for rilpivirine 25 mg tablets approved May 20, 2011) and Viread® (NDA 21-356 for tablet formulation approved on 26 October 2001), respectively. In the United States, emtricitabine and tenofovir disoproxil fumarate are approved for use in adolescents. An oral solution of emtricitabine is approved in the United States and may be administered to newborns.

Emtricitabine and tenofovir disoproxil fumarate are approved for the treatment of HIV-1 infection in a fixed-dose combination product Truvada® (NDA 21-752 for tablet formulation approved on 2 August 2004). Emtricitabine, tenofovir disoproxil fumarate and efavirenz (a nonnucleoside reverse transcriptase inhibitor) are approved in a fixed-dose combination as Atripla® (approved for use in the US on 12 July 2006).

3 Studies Submitted

3.1 Studies Reviewed

All nonclinical information for the current NDA is cross-referenced to the original NDAs and INDs and no additional nonclinical toxicology information is included in the submission package. Refer to applicable sections of Gilead NDA 21-500, NDA 21-896 and Gilead IND 53,971 for FTC, Gilead NDA 21-356 and IND 52,849 for TDF and by right of cross-reference to Tibotec NDA 202022 and IND 67,699 for RPV.

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

/s/

MARK J SEATON
07/07/2011

HANAN N GHANTOUS
07/08/2011
I concur with the primary nonclinical reviewer, Dr. Mark Seaton on teh approval of this combination.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-123 **Applicant:** Gilead **Stamp Date:** February 10, 2011

Drug Name: FTC/RPV/TDF **NDA/BLA Type:** Combination

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		*Acceptability of revised certificate of analysis will be a Quality/CMC decision*
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

MARK J SEATON
03/16/2011

HANAN N GHANTOUS
03/17/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202-123 **Applicant:** Gilead **Stamp Date:** November 23, 2010

Drug Name: FTC/RPV/TDF **NDA/BLA Type:** Combination

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? No

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Issues remain regarding a secondary degradation product, called (b) (4), related to the emtricitabine drug substance. The sponsor must provide confirmatory evidence describing levels of (b) (4) in test article from the previous qualification study titled *"A 14-Day Oral Gavage Study Comparing Non-Degraded and Degraded TDF/FTC in Sprague-Dawley Rats"*. The evidence should describe (b) (4) levels present at the time the study was conducted. Absent that confirmatory evidence, an additional qualification study may be required.

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

Please provide confirmatory evidence describing levels of (b) (4) (b) (4) in test article from the previous qualification study titled *"A 14-Day Oral Gavage Study Comparing Non-Degraded and Degraded TDF/FTC in Sprague-Dawley Rats"*. The evidence should describe (b) (4) levels present at the time the study was conducted. Absent that confirmatory evidence, an additional qualification study may be required.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Pharmacologist	Date
Team Leader/Supervisor	Date

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

/s/

MARK J SEATON
01/13/2011

HANAN N GHANTOUS
01/13/2011