

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-937

MICROBIOLOGY REVIEW(S)

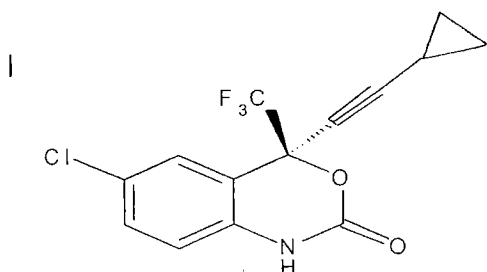
Microbiology Review
Division of Antiviral Drug Products (HFD-530)

NDA#: 21-937 Serial #: 000 Reviewer: N. Battula, Ph.D.

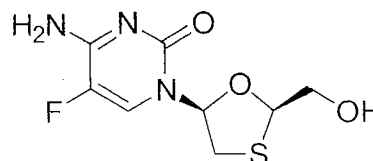
Date submitted: April 26, 2006 Date review completed: June 15, 2006

Sponsors: Gilead Sciences.
 333 Lakeside Drive
 Foster City, CA 94404
 and
 Bristol-Myers Squibb
 Rt.206, Provinceline Road
 PO Box 400
 Princeton, NJ 08543

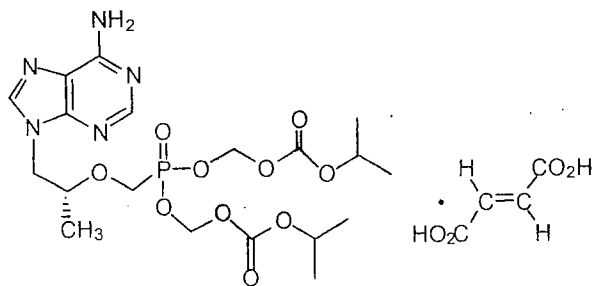
Product name(s): Atripla™ tablet is a fixed-dose combination product as a solid tablet containing three active pharmaceutical ingredients efavirenz, emtricitabine and tenofovir disoproxil fumarate. Some of the chemical characteristics of the three drug substances are listed below.



Proprietary name: SUSTIVA®
Nonproprietary name: Efavirenz
Chemical name: (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one
Molecular formula: C₁₄H₉ClF₃NO₂
Molecular mass: 315.68
Dosage form: 600 mg tablet
Route of administration: Oral



Proprietary name: EMTRIVA®
Nonproprietary name: Emtricitabine
Chemical name: 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine
Molecular formula: C₈H₁₀FN₃O₃S
Molecular mass: 247.24
Dosage form: 200 mg tablet
Route of administration: Oral



Proprietary name: VIREAD[®]

Nonproprietary name: Tenofovir DF

Chemical name: 9-[(R)-2-[[bis[[isopropoxy carbonyl]oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1)

Molecular formula: C₈H₁₀FN₃O₃S

Molecular mass: 247.24

Dosage form: 200 mg tablet

Route of administration: Oral

Dosage form: Film-coated tablet (immediate-release solid)

Route of administration: Oral, single tablet once a day

Indication: Treatment of HIV-1 infection in adults

Related documents: INDs 49,465 for efavirenz, 53,971 for emtricitabine, 52,849 for Tenofovir DF and 67,671 for emtricitabine/tenofovir DF combination product, and the NDAs 20-972 and 21-360 for Sustiva[®], 21-500 for Emtriva[®], 21-356 for Viread[®] and 21-752 for the emtricitabine/tenofovir DF combination product, Truvada[®].

Background and Summary: In a joint venture partnership two pharmaceutical sponsors, Bristol-Myers Squibb and Gilead Sciences, LLC, submitted this NDA in support of a fixed dose combination tablet containing three active pharmaceutical ingredients: Efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg, for the treatment of HIV-1 infection in adults. Each of the components in the fixed dose combination tablet, efavirenz (EFV), emtricitabine (FTC) and tenofovir disoproxil fumarate (T DF) are approved at the same dosage as in the proposed fixed dose combination tablet for the treatment of HIV-1 infection in combination with other antiretroviral agents. In addition, a fixed dose combination of 200 mg of emtricitabine

and 300 mg of tenofovir DF is also approved for the treatment of HIV-1 infection in adults. For the triple drug fixed dose combination tablet the applicants are seeking the indication for the use of Atripla™ alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

Microbiology evaluations including the mechanism of action, antiviral activities, resistance and cross-resistance studies for the INDs and NDAs (of each of the drug substance efavirenz, emtricitabine and tenofovir DF and their corresponding drug products, Sustiva®, Emtriva® and Viread® have been reviewed and documented. In addition, a two drug fixed dose combination tablet, Truvada®, containing tenofovir DF/emtricitabine is also approved for the treatment of HIV-1 infection in combination with other antiretroviral agents. The salient features of each of the drugs mechanism action, antiviral activities, non-clinical and clinical resistance and cross-resistance are incorporated in their respective package inserts. For additional details please see the microbiology reviews for the products in their respective IND and NDA submissions.

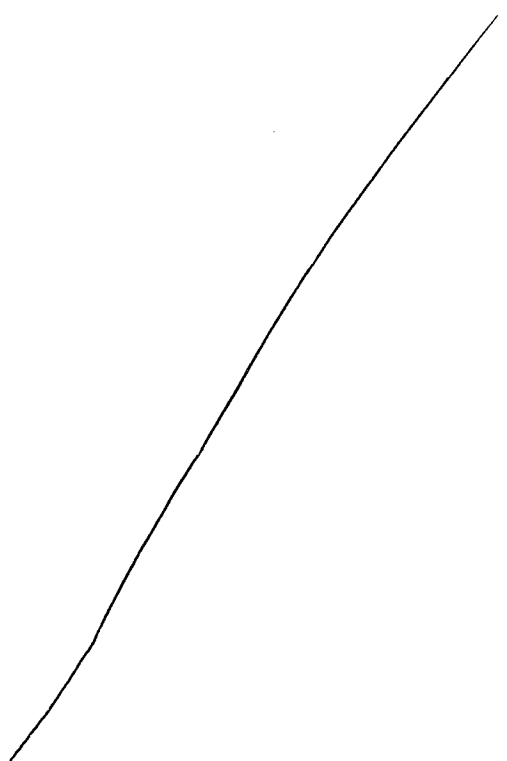
In support of the application for Atripla™ the EFV/FTC/TDF film-coated tablet, the sponsors conducted bioequivalence studies in healthy subjects evaluating the bioequivalence of the proposed commercial fixed dose formulation of the EFV/FTC/TDF combination tablet and a 600 mg tablet of efavirenz, a 200 mg capsule of emtricitabine, and a 300mg tablet of tenofovir DF taken concurrently under fasted conditions. Based on the results of the bioequivalence studies the sponsors concluded that one EFV/FTC/TDF fixed dose film-coated tablet was bioequivalent to one efavirenz tablet (600 mg) plus one emtricitabine tablet (200 mg) plus one tenofovir DF tablet (300 mg, equivalent to 245 mg of tenofovir disoproxyl) administered concurrently. For detailed review and evaluation of bioequivalence studies see the clinical pharmacology review by Dr. J. DiGiacinto.

Conclusions: Microbiology reviews and evaluations including the mechanism of action, antiviral activities, resistance and cross-resistance of the INDs and NDAs for each of the drug substance, efavirenz, emtricitabine and tenofovir DF and their corresponding drug products Sustiva®, Emtriva®, Viread® have been documented. In addition, a two drug fixed dose combination tablet, Truvada®, containing tenofovir DF/emtricitabine is also approved for the treatment of HIV-1 infection in combination with other antiretroviral agents. In this NDA for the fixed-dose combination product Atripla™ the sponsors submitted bioequivalence data evaluating the bioequivalence of the commercial formulation of the EFV/FTC/TDF tablet, and a 600 mg tablet of efavirenz, a 200 mg capsule of emtricitabine, and a 300 mg tablet of tenofovir taken concurrently under fasted conditions. In the proposed microbiology portion of the package insert the individual microbiology package inserts for Sustiva®, Emtriva®, Viread® are presented with reordering of some sentences and minor modifications to reflect consistency. The

microbiology portion of the package insert was revised and the version agreed upon by the sponsors and the FDA is presented below.

Recommendations: Each of the individual drugs in Atripla™ combination tablet (EFV/FTC/TDF) is approved for the treatment of HIV-1 infection in combination with other antiretroviral agents. In addition, the combination tablet of Truvada® (TDF/FTC) is also approved for the treatment of HIV-1 infection in combination with other antiretroviral agents. The approvals were based on the demonstration of anti-HIV-1 activity and improvement in CD4 cells in clinical studies. There are no microbiology issues with respect to Atripla™. From the microbiology perspective Atripla™ is recommended for approval.

Microbiology portion of the package insert for Atripla™



4 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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/s/

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