CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-896

PHARMACOLOGY REVIEW

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-896**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**03/29/05**
PRODUCT:	**Emtricitabine**
INTENDED CLINICAL POPULATION:	**Treatment of HIV-1 infection in pediatric patients**
SPONSOR:	**Gilead Sciences, Inc.**
DOCUMENTS REVIEWED:	**Electronically**
REVIEW DIVISION:	**Division of Antiviral Drug Products (HFD-530)**
PHARM/TOX REVIEWER:	**Pritam S. Verma, Ph.D.**
PHARM/TOX SUPERVISOR:	**James G. Farrelly, Ph.D.**
DIVISION DIRECTOR:	**Debra Birnkrant, M.D.**
PROJECT MANAGER:	**Jeff O'Neill**

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: There are no nonclinical pharmacology and toxicology issues which would preclude the approval of this NDA.

B. Recommendation for nonclinical studies: To support clinical use, the nonclinical toxicity profile of emtricitabine was characterized in an extensive battery of in vitro and in vivo studies including carcinogenicity studies in rats and mice. The pivotal toxicology studies supporting the safety of emtricitabine were appropriately designed and conducted in compliance with Good Laboratory Practice (GLP) regulations. In conclusion, the results of extensive nonclinical toxicology and pharmacokinetic evaluation programs support the proposed use of emtricitabine in humans.

C. Recommendations on labeling: The label is modified to include results of the carcinogenicity studies.

II. Summary of nonclinical findings

A: Brief overview of nonclinical findings: A comprehensive nonclinical safety pharmacology, ADME and toxicology program has been undertaken in support of the registration of emtricitabine for the treatment of HIV infection in adults. The results of this evaluation have been presented in detail in the original NDA for Emtriva (emtricitabine) capsules (NDA 21-500). No new nonclinical Pharmacology, Pharmacokinetics, or Toxicology studies have been undertaken in support of this application.

B. Pharmacological activity: No new studies were reported.

C. Nonclinical issues relevant to clinical use: The Exec CAC concluded that emtricitabine produced no tumors in rats and mice. Emtricitabine can be classified as Pregnancy Category B. Emtricitabine should be used during pregnancy only if clearly needed.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

Emtricitabine (Emtriva, FTC) is an approved nucleoside reverse transcriptase inhibitor (NRTI) administrated once daily (QD) in combination with other antiretroviral agents for the treatment of HIV-1 infection. Emtricitabine as a capsule formulation was first approved in the United States on 02 July 2003 for the treatment of adults with HIV-1 infection in combination with other antiretroviral agents. The 200 mg emtricitabine capsule formulation is approved for marketing in the United States for the treatment of adult HIV-1 infection under NDA 21-500.

While the emtricitabine capsule formulation is approved for marketing in the United States for the treatment of adult HIV-1 infection under the NDA 21-500, this application addresses the use of the capsule and oral solution (10 mg/mL, 200 mg emtricitabine) in the pediatric setting. This New Drug Application (NDA) provides an overview and the results of the pediatric development program conducted in support of emtricitabine for use in combination with other antiretroviral agents in the treatment of HIV-1 infection in pediatric patients.

NDA number: 21-896

Review number: 000

Sequence number/date/type of submission: 000/03/29/05/N

Information to sponsor: No

Sponsor and/or agent: Gilead Sciences, Inc.
Foster City, CA 94404

Manufacturer for drug substance: [redacted]

Abbott Laboratories
Specialty Products Division
1401 Sheridan Road
North Chicago, IL 60064

Reviewer name: Pritam S. Verma, Ph.D.

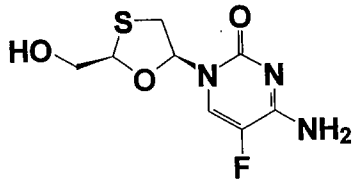
Division name: Division of Antiviral Drug Products

HFD #: 530

Review completion date: 4/20/05

Drug:

Trade name: Emtriva[R]
Generic name: Emtricitabine
Code name: 524W91, FTC
Chemical name: 4-Amino-5-fluoro-1-(2R-hydroxymethyl-[1,3]oxathiolan-5S-yl)-(1H)-pyrimidin-2-one
CAS registry number: 143491-57-0
Molecular formula: $C_8H_{10}FN_3O_3S$
Molecular weight: 247.24
Structure:



Relevant IND: 53,971

Relevant NDA: 21-500

Drug class: Nucleoside analog

Intended clinical population: Treatment of HIV-1 infection in pediatric patients

Clinical formulation: oral solution, 10 mg/ml

Route of administration: oral

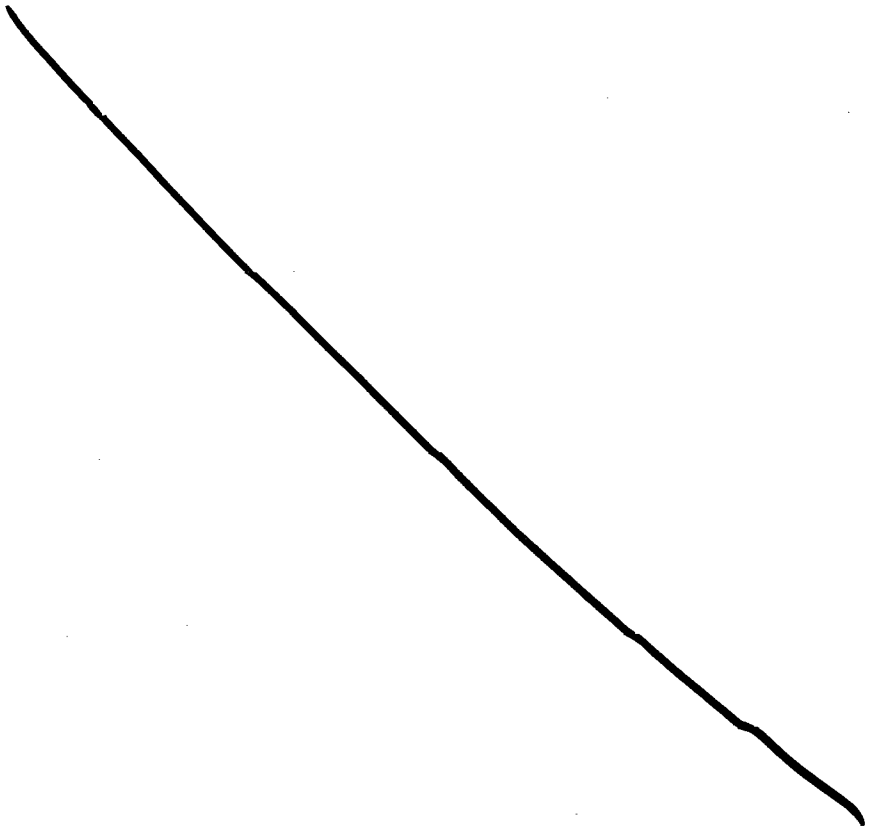
Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

NONCLINICAL TOXICOLOGY

All pharm/tox information contained in NDA 21-500 is incorporated by cross-reference to NDA 21-896. Please see the review of NDA 21-500. The issue of label is discussed below:

LABEL:

Carcinogenesis, Mutagenesis, Impairment of fertility:



OVERALL conclusions and recommendations

Conclusions: To support clinical use, the nonclinical toxicity profile of emtricitabine was characterized in an extensive battery of in vitro and in vivo studies including carcinogenicity studies in rats and mice. The pivotal toxicology studies supporting the safety of emtricitabine were appropriately designed and conducted in compliance with Good Laboratory Practice (GLP) regulations. The results of nonclinical toxicology studies do not suggest any special safety issues for humans taking emtricitabine. In conclusion, the results of extensive nonclinical toxicology and pharmacokinetic

evaluation programs support the proposed use of emtricitabine in humans.

Unresolved toxicology issues (if any): None

Recommendations: There are no nonclinical pharmacology and toxicology issues which would preclude the approval of this NDA.

Suggested labeling: The label is modified to include results of the carcinogenicity studies in rats and mice.

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

Attachment: Minutes of Exec CAC

Executive CAC

Date of Meeting: August 10, 2004

Committee: David Jacobson-Kram, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Abigail Jacobs, Ph.D., HFD-024, Member
Chuck Resnick, Ph.D., HFD-110, Alternate Member
James G. Farrelly, Ph.D., HFD-530, Team Leader
Pritam S. Verma, Ph.D., HFD-530, Presenting Reviewer

Author of Draft: Pritam S. Verma, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review [NDA 21-500 N-000 4F].

IND #: 53,971

Drug Name: Emtriva

Sponsor: Gilead Sciences, Inc.

Background: Emtriva (also known as FTC), a synthetic nucleoside analog of cytosine, is phosphorylated by cellular enzymes to form [redacted]

inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5-triphosphate by being incorporated into nascent viral DNA resulting in chain termination. Emtriva is indicated for the treatment of HIV-1 infection.

The safety pharmacology, general toxicology, genotoxicology and reproductive toxicology studies of FTC had been characterized in a variety of animal species. In the general toxicology studies, FTC was well tolerated for up to a year at doses producing systemic exposures much greater than those produced in patients at the recommended 200 mg daily dose. Toxicity was limited to animals in the high dose group resulting in mild reversible anemia in mice at 3000 mg/kg/day (6 months) and soft feces in female monkeys at 2000 mg/kg/day (1 month). FTC was not genotoxic, and it did not adversely affect reproduction or embryo fetal development. The sponsor received prior CAC concurrence for the protocols for the rat and mouse carcinogenicity studies. Dose selection was based on a >25-fold multiple of the human exposure.

Rat Carcinogenicity Study: The oncogenic potential of emtriva was investigated in male and female CD rats at oral gavage dosages of 60 (low), 200 (mid) or 600 mg/kg/day (high) in comparison with vehicle controls for a period of 104 weeks.

No drug-related neoplasms were seen in the rat study.

Mouse Carcinogenicity Study: The oncogenicity potential of emtriva was investigated in CD-1 mice at oral gavage dosages of 80 (low), 250 (mid) or 750 mg/kg/day (high) in comparison with vehicle controls for a period of 104 weeks.

No drug related neoplasms were seen in the mouse study.

Executive CAC Recommendations and Conclusions:

The CAC committee found the carcinogenicity studies in rats and mice to be acceptable. The committee noted that the protocols had been approved by the Exec CAC. The committee concurred that no drug-related neoplasms were seen in rats or mice.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-530
/JFarrelly, HFD-530
/PVerma, HFD-530
/MHolloman, HFD-530
/ASeifried, HFD-024

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/s/

Pritam Verma
5/11/05 08:40:18 AM
PHARMACOLOGIST

James Farrelly
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