CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-500

Chemistry Review(s)

FINAL

NDA 21-500

Emtriva® (emtricitabine) Capsules

Gilead Sciences, Inc.

George Lunn
Division of Anti-Viral Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-500

2. REVIEW #1

3. REVIEW DATE: 5-Jun-2003

4. REVIEWER: George Lunn

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	20-Aug-2002
Amendment (BC)	26-Sep-2002
Amendment (BC)	15-Oct-2002
Amendment (BC)	26-Feb-2003
Amendment	25-Apr-2003
Amendment	28-Apr-2003
Amendment	29-Apr-2003
Amendment	09-May-2003
Amendment	20-May-2003
Amendment	23-May-2003
Amendment	06-Jun-2003
Amendment	20-Jun-2003
Amendment	25-Jun-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404
Representative:	Martine Kraus, Ph.D. Director, Regulatory Affairs
Telephone:	(650) 522 5722

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Emtriva [originally submitted as Coviracil]
b) Non-Proprietary Name (USAN): emtricitabine
c) Code Name/# (ONDC only): FTC; TP-0006; A-319807.0; D19807; 25053
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

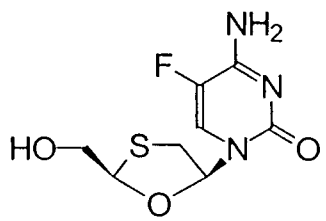
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

__X__SPOTS product – Form Completed

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-Fluoro-1-[(2R,5S)-2-(hydroxymethyl)[1,3]oxathiolan-5-yl]cytosine
4-amino-5-fluoro-1-(2R-hydroxymethyl[1,3]oxathiolan-5S-yl]-(1H)-pyrimidin-2-one
(-)-2',3'-Dideoxy-5-fluoro-3-thiacytidine



Registry Number [143491-57-0]

$C_8H_{10}FN_3O_3S$ Formula Weight: 247.24

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV		Gelatin capsules	1	Adequate	12/30/02	Reviewed by G. Lunn
	III		bottle	3	Adequate	5/28/02	Review by J. Boal, adequate for a solid oral dosage form
	III		bottle :	3	Adequate	5/7/99	Review by R.S. Harapanhalli, adequate for a bottle
	III		induction seal	4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	25-Jun-2003	B. Merritt, OC, CDER
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 21-500

The Executive Summary

I. Recommendations

- **A. Recommendation and Conclusion on Approvability**

  This NDA is recommended for approval from the CMC perspective.

- **B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approval**

  None

II. Summary of Chemistry Assessments

- **A. Description of the Drug Substance and Drug Product**

Drug Substance

Emtricitabine is an NME reverse-transcriptase inhibitor for the treatment of HIV infection. Emtricitabine is a single enantiomer with two chiral centers. It is a white to off-white water-soluble powder. Three polymorphic forms have been identified but only the most stable Form I is produced by the synthesis, and will be used as the drug substance. The structure of FTC is determined by analysis.

As originally proposed by the sponsor the starting materials were At the request of the FDA the sponsor opted to designate as starting materials, The specifications for these compounds are reasonable. The synthesis is well described.

The reactions are well controlled and the isolated intermediates have comprehensive and appropriate specifications. An early problem that resulted in has been overcome.

The drug substance specifications are comprehensive and appropriate and include specifications for assay, water, residual solvents, particle size, impurities, and chiral purity. At the request of

FDA the limits for ; ——— were reduced from ——— , and the limit for the enantiomer was reduced from —— Although rather high the limit for the enantiomer is toxicologically qualified and corresponds to current manufacturing capability. The specifications are justified based on toxicological considerations and the characteristics of 12 recent lots of drug substance made at the commercial site. The analytical methods are described in detail and have been validated.

Late in the review process ——— was introduced as an alternate drug substance manufacturing site. Five lots manufactured by —— are compared to 12 lots manufactured at the original site —— and are shown to be similar.

Based on 24 months (3 batches) and 21 months (1 batch) of long-term and 6 months (4 batches) of accelerated stability data on batches manufactured on full to quarter scale, a retest date of 24 months is assigned.

Drug Product

The drug product is a capsule containing 200 mg emtricitabine with microcrystalline cellulose, crospovidone, povidone, and magnesium stearate as inactive ingredients. The inactive ingredients are compendial and the capsule shells are covered by a DMF from ——

The capsules are manufactured using ——— The manufacturing process is described in detail and the in-process controls are appropriate.

The specifications are appropriate and contain tests for identity, assay, degradants, water, weight variation, dissolution, and aerobic microbial count. Justifications are provided for the specifications. The analytical methods are described in detail and validated. However, discussion of the analytical methods is extremely fragmented. Numerous reports are supplied for each method. Tier 2 testing using an enzyme is provided for the dissolution method. However, Tier 2 testing has not yet been required.

The commercial product will contain 30 capsules in a —— bottle with a child-resistant —— closure and an induction seal. Late in the review process an alternate container-closure system was described. The alternate system is similar but consists of components from different manufacturers. Either system is acceptable.

The stability data are generally satisfactory. Although some slowing in dissolution was observed for one batch there were no failures. The sponsor feels that the problem has been solved ———

The sponsor supplies data to show that this product qualifies for a categorical exclusion from the requirement to file an Environmental Assessment.

A complete Methods Validation package is supplied. The methods have been supplied to FDA laboratories but the results are not expected prior to the approval of this NDA.

An Establishment Evaluation Request was submitted and an overall recommendation of Acceptable has been received.

- **B. Description of How the Drug Product is Intended to be Used**

Emtricitabine is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection. The recommended daily dose is one 200 mg capsule. Emtricitabine is supplied as a package of 30 capsules in —— bottle.

An expiration dating period of 24 months is approved, based on 24 months of long-term stability data for one large scale, one pilot scale, and 3 small scale lots and 18 months of long-term stability data for one large scale lot. These data also support the storage statement, "Store at 25 °C (77 °F); excursions permitted to 15 °C – 30 °C (59 °F - 86 °F) (see USP Controlled Room Temperature)".

- **C. Basis for Approvability or Not-Approval Recommendation**

The drug substance manufacturing process is well controlled and described in detail. The specifications are appropriate and justified and the retest date is supported by appropriate data. The composition, manufacturing process, and specifications for the capsules are appropriate and the expiration dating period is supported by adequate data. The container-closure system and labeling are appropriate. After evaluation all manufacturing sites were found to be acceptable. This NDA is therefore recommended for approval from a CMC perspective.

III. Administrative

- **A. Reviewer's Signature**

George Lunn, Ph.D. {Signed Electronically in DFS} Date of draft review 6/5/03

- **B. Endorsement Block**

Stephen P. Miller, Ph.D.

- **C. CC Block**

Chi-wan Chen, Ph.D.

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secret and/or

confidential

commercial

information

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

/s/

George Lunn
6/27/03 04:01:05 PM
CHEMIST

FTC Review (with EES report)

Stephen Paul Miller
6/27/03 04:14:14 PM
CHEMIST