CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-896

CHEMISTRY REVIEW(S)

NDA 21-896

Emtriva (emtricitabine) Oral Solution

Gilead Sciences, Inc.

George Lunn, Ph.D.
Division of Anti-Viral Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA 21-896

2. REVIEW #: 1

3. REVIEW DATE: 19-Sep-05

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA [redacted] (withdrawn)	3-Sep-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-Mar-2005
Amendment	15-Apr-2005
Amendment	25-Apr-2005
Amendment	25-Jul-2005
Amendment	12-Sep-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404

Chemistry Review Data Sheet

Representative: Pamela Danagher, M.Sc.
Associate Director, Regulatory Affairs

Telephone: 650 522-6395
(fax) 650 522-5489

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Emtriva Oral Solution
b) Non-Proprietary Name (USAN): emtricitabine oral solution
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 2
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-HIV

11. DOSAGE FORM: Oral solution

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

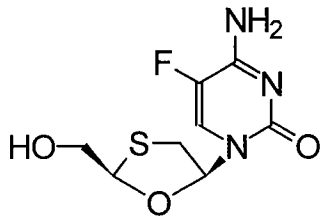
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___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
[redacted]	IV	[redacted]		1	Adequate	25-Aug-2005	Review by G. Lunn

[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	21-Sep-2005	J. D'Ambrogio, OC
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-896

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been satisfactorily resolved and an overall recommendation of Acceptable has been made by the Office of Compliance.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Chemistry, manufacturing, and controls information for emtricitabine drug substance is contained in the approved NDA 21-500, as amended, for Emtriva (emtricitabine) capsules and is incorporated by reference. Drug substance may be manufactured using [redacted]

All facilities were found to be acceptable based on profile or file review except for the [redacted] facility. An inspection of this facility was conducted and it was found to be satisfactory. An overall recommendation of Acceptable was made by the Office of Compliance.

Emtricitabine oral solution is a clear, orange to dark-orange liquid in a buffered, flavored aqueous formulation for oral administration. Each 1 mL solution contains 10 mg emtricitabine. The solution is packaged in [redacted] bottles with child-resistant closures. The deliverable volume is 170 mL. Inactive ingredients are cotton candy flavor, [redacted] FD&C yellow No. 6, hydrochloric acid, methylparaben, [redacted], propylene glycol, propylparaben, purified water, sodium hydroxide, and xylitol. A justification for the use of each excipient is provided. A formulation development report is

provided. The total propylene glycol concentration is [redacted] The recommended pediatric dose is 6 mg/kg/day. This corresponds to a daily dose of 0.6 mL solution per kg per day or [redacted] of propylene glycol, less than the WHO limit of [redacted]/day.

Drug product manufacture, packaging, labeling, and release testing will take place at Abbott Laboratories, North Chicago, IL. Drug product labeling, release testing, and release will take place at Gilead Sciences, Ltd., Blackrock, Ireland and Gilead Sciences, Inc., San Dimas CA. Stability testing will take place at San Dimas. The facility in Ireland was inspected and found to satisfactory. The other facilities were found to be satisfactory based on profile or file review. An Overall Rating of Acceptable was made by Compliance.

A flow diagram is provided and a detailed description of the manufacturing procedure are provided. The commercial batch size is [redacted] Critical steps have been identified and appropriate controls are applied. The process was validated by the manufacture of three consecutive [redacted] batches by Abbott Laboratories. [redacted] In this way lot homogeneity was demonstrated and the process is considered validated. Satisfactory batch analyses are provided for these batches. No reprocessing operations are planned.

All excipients except the FD&C Yellow No. 6 color and the Cotton Candy Flavor are compendial USP/NF grade. The Cotton Candy Flavor is covered by a DMF. A Letter of Authorization to refer to this DMF is provided. The DMF has been reviewed and this flavor has been found to be adequate for use in a pharmaceutical product. The dye is tested according to 21 CFR 82.706. A copy of the FDA certification of one batch is provided.

A comprehensive specification is provided which includes tests for appearance, identity of emtricitabine (by HPLC and TLC), identity of parabens (by HPLC), pH, deliverable volume, assay, degradants [redacted] unspecified, and total), methylparaben, propyl paraben, and microbial limits. The acceptance criteria are appropriate. A full justification of the specifications is provided. Generally the specifications are conventional for an oral liquid. The pH range ensures the stability of the paraben preservatives. There is a slow loss in assay for the parabens with time. Tests showed that paraben levels of [redacted] of the nominal value still provided anti-microbial effectiveness. Therefore the lower limit of [redacted] is justified. Under normal storage conditions the only degradant observed is [redacted] The maximum observed after 36 months at the normal storage conditions of 5°C is 0.36% and after [redacted] months at the accelerated storage conditions of 25°C/40% RH is [redacted]. Other potential degradants are covered by the unspecified impurities limit [redacted] Unspecified degradants have been observed at up to [redacted] The maximum level of total impurities observed after 36 months at the normal storage conditions of 5°C is [redacted] and after [redacted] months at the accelerated storage conditions of 25°C/40% RH is [redacted] This justifies the total impurities limit of [redacted]

The analytical methods are described in detail and have been appropriately validated.

Satisfactory batch analyses are provided for [redacted] batches manufactured on the commercial [redacted] scale.

An amber [redacted] bottle with a child-resistant closure was chosen. A [redacted] dosing cup with graduations is also supplied. The product contact materials conform with the applicable sections of 21 CFR for food-contact applications.

Thirty six months of satisfactory long-term stability data obtained at 5°C are presented for 3 batches [redacted] months of satisfactory data are presented for 3 batches, an[redacted] months of satisfactory data are presented for 2 batches. In additio[redacted] months of satisfactory accelerated data obtained at 25°C/40% RH are presented for 3 batches and 3 months of satisfactory data are presented for 2 batches. There are no out of specification results. The only obvious trends are to increasing amounts of degradants and decreasing amounts of preservatives with time and temperature. One batch was stored in the [redacted] container and in the commercial container-

[redacted]

In the original NDA the storage statement was "Store refrigerated, 2-8°C (36-46°F)". At the request of FDA this storage statement was elaborated to indicate that the product may be stored at room temperature for a short period before use. The final agreed storage statement is "Store refrigerated, 2-8°C (36-46°F). The Emtriva Oral Solution should be used within 3 months if stored by the patient at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)". The equivalent statement in the Patient Package Insert is "Store Emtriva Oral Solution in a refrigerator between 36 and 46°F (2-8°C). Do not freeze. Alternatively, the product may be stored at room temperature for up to 3 months and any remaining solution in the bottle must be discarded after the 3 months". These statements are supported by the stability data.

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

Emtriva Oral Solution is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection. Emtriva Oral Solution contains 10 mg/mL emtricitabine. The recommended dose is 6 mg/kg up to a maximum of 240 mg (24 mL) administered once daily orally. The oral solution is supplied in a 170 mL amber [redacted] bottle with a child-resistant closure. A single bottle provides approximately 28 day of dosing for a 10-kg patient, and 7 days for a 40-kg patient (at the maximum dose). A [redacted] dosing cup with graduations is also supplied. The storage recommendation is "Store refrigerated, 2-8 °C (36-46 °F). Emtriva Oral Solution should be used within 3 months if stored by the patient at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)". The expiration dating period is 36 months.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for emtricitabine drug substance are described in approved NDA 21-500 for Emtriva (emtricitabine) capsules, as amended. The composition, manufacturing process, controls, and specification for the oral solution are appropriate and the expiration dating period of 36 months is supported by adequate data. The container-closure system and labeling are appropriate. All manufacturing sites have been 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}

B. Endorsement Block

Stephen P. Miller, Ph.D. FFTL {Signed Electronically in DFS}

C. CC Block

Norman R. Schmuff, Ph.D.

44 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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
9/23/2005 11:18:29 AM
CHEMIST

Emtricitabine oral solution

Stephen Paul Miller
9/23/2005 11:27:46 AM
CHEMIST
NDA 21-896 is recommended for approval from the CMC perspective.