CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-937

CHEMISTRY REVIEW(S)

NDA/ANDA 21-937

ATRIPLA

Bristol-Myers Squibb & Gilead Sciences LLC

George Lunn
Division of Anti-Viral Products

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 11

C. Basis for Approvability or Not-Approval Recommendation 11

III. Administrative 12

A. Reviewer's Signature 12

B. Endorsement Block 12

C. CC Block 12

Chemistry Assessment 13

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 13

S DRUG SUBSTANCE 13

P DRUG PRODUCT — Tablets] 16

A APPENDICES 69

R REGIONAL INFORMATION 69

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 70

A. Labeling & Package Insert (Amendment of 4/5/06) 70

B. Environmental Assessment Or Claim Of Categorical Exclusion 70

III. List Of Deficiencies To Be Communicated 70

IV. EES Report 72

Chemistry Review Data Sheet

1. NDA or ANDA 21-937

2. REVIEW #: 1

3. REVIEW DATE: 05-May-2006

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	24-Mar-2006
Amendment	05-Apr-2006
Amendment	18-Apr-2006
Amendment	25-Apr-2006
Amendment	03-May-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Bristol-Myers Squibb & Gilead Sciences LLC

Chemistry Review Data Sheet

Address:	Gilead Sciences 333 Lakeside Drive Foster City CA 94404
Representative:	Pamela Danagher, M.Sc.
Telephone:	650 522 6395; fax 650 522 5489

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: —
b) Non-Proprietary Name (USAN): efavirenz/emtricitabine/tenofovir disoproxil fumarate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 4
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Treatment of HIV

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300 mg

13. ROUTE OF ADMINISTRATION: Oral

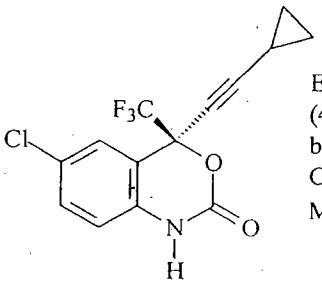
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

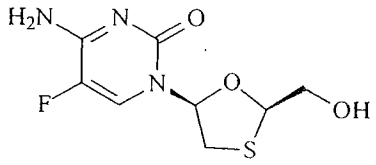
Chemistry Review Data Sheet

___X___Not a SPOTS product

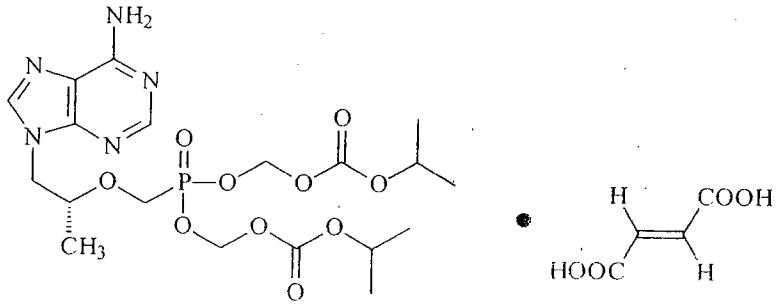
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Efavirenz
(4S)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one
$C_{14}H_9ClF_3NO_2$
MW: 315.67



Emtricitabine
5-Fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine
$C_8H_{10}FN_3O_3S$
MW: 247.24

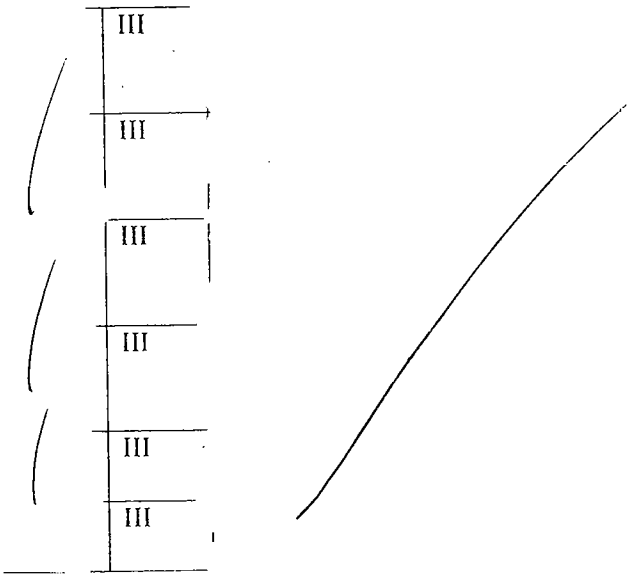


•Tenofovir disoproxil fumarate
9-[(R)-2[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1)
$C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$
MW: 635.51

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS



4	Adequate		
4	Adequate		
4	Adequate		
4	Adequate		
4	Adequate		
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:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Biometrics	N/A		
EES	Acceptable	3-May-2006	J. D'Ambrogio
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not required		
OPDRA	N/A		
EA	Not required		
Microbiology	N/A		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

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:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-937

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)

The chemistry, manufacturing, and controls for efavirenz drug substance are described in approved NDAs 20-972 for Sustiva (efavirenz) Capsules and 21-360 for Sustiva (efavirenz) Tablets. The chemistry, manufacturing, and controls for tenofovir disoproxil fumarate drug substance are described in approved NDAs 21-356 for Viread (tenofovir disoproxil fumarate) Tablets and 21-752 for Truvada (emtricitabine/ tenofovir disoproxil fumarate) Tablets. The chemistry, manufacturing, and controls for emtricitabine drug substance are described in approved NDAs 21-500 for Emtriva (emtricitabine) capsules and 21-752 for Truvada (emtricitabine/ tenofovir disoproxil fumarate) Tablets.

The drug product is a tablet containing a fixed dose combination of efavirenz (600 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (tenofovir DF) (300 mg). The tablets

The tablets are approximately 20 mm long and 10.4 mm wide. The tablets are pink, capsule-shaped, film-coated tablets debossed with 123 on one side and plain on the other.

Inactive ingredients are croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, film coat, sodium lauryl sulfate, All excipients are compendial USP/NF grade except for the film coatings. The film coatings are comprised of USP/NF grade materials except for the iron oxide black which conforms to 21 CFR 73.1200. The magnesium stearate is of vegetable origin.

A letter to this effect from the supplier is provided. The manufacturer also provides letters indicating that no components of the film-coating materials come from animals.

An alternative trade dress is also proposed for export.

Manufacturing and packaging are identical to those used for the US product.

A pharmaceutical development section is provided. A number of formulations were tried before a formulation that was bioequivalent to the separate currently-marketed tablets was developed. The final formulation is bioequivalent to the currently approved Sustiva and Truvada tablets. It is quite similar in composition although with amounts of excipients compared to the separate tablets. are omitted.

All manufacturing sites have been found to be acceptable, some after inspections. On 5/3/06 an Overall Recommendation of Acceptable was made by J. D'Ambrogio, OC.

The manufacturing process consists of an

A detailed narrative of the manufacturing process, with actual quantities as used to manufacture a typical commercial batch of tablets, is supplied. The controls on the critical steps are adequately described. Executed batch records for the manufacture of a primary stability batch on a scale are provided.

The applicant reports that process validation is shown by the manufacture of three batches and one batch. Process validation will be completed during the manufacture of the commercial scale batches.

An adequate drug product specification is provided. Tests for appearance, identity of actives, assay, impurities, content uniformity, and dissolution are included. Generally the specifications are the same as those for the approved NDAs for Sustiva (efavirenz) and Truvada (emtricitabine and tenofovir DF). A new impurity, , is specified. This is qualified at , more than the acceptance criterion of The qualification levels for the other specified impurities were established in the previous NDAs. No new impurities or degradants have been identified in these tablets. Descriptions of the impurities and degradants are contained in the approved NDAs for Sustiva, Emtriva, and Truvada. A justification for the specifications is provided. Generally the specifications are the same as those for the approved Sustiva and Truvada NDAs.

The analytical methods are described in detail and have been adequately validated. The method for impurities is essentially the Truvada method with the so as to efavirenz and its related impurities. The dissolution method uses 2% sodium lauryl sulfate in water. This is similar to the Sustiva (efavirenz) method. Efavirenz is the least soluble active. The Truvada (emtricitabine and tenofovir DF) method uses 10 mM HCl.

Satisfactory batch analyses are provided for 4 batches (three — and one — .

The container closure system consists of a white HDPE bottle fitted with a — child-resistant closure and an — Each bottle contains 30 tablets and —, of silica gel — canister. Each component is covered by a DMF and a Letter of Authorization to refer to each DMF is provided. In addition, all drug contact components comply with the relevant 21 CFR indirect food contact regulations. Therefore no review of the DMFs is required. Test parameters for each component are provided. The container labels for the US version and the export version are provided. Labels bearing the alternate trade names — and "Atripla" are provided. Either is acceptable from a CMC point of view.

— , of satisfactory stability data are supplied for tablets stored at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH. A statistical analysis is provided. In addition — s of satisfactory data are provided for the tablets stored at the ICH Q1F conditions of 25°C/80% RH and 50°C/ambient RH, in an — for — , and in the —

No out of specification results are observed except that the — degradant — was — after — at 50°C/ambient RH exceeding the limit of — . The only trends observed are a trend to greater degradants, particularly the — with time and temperature. After — at 50°C/ambient RH lower assay values are also seen for emtricitabine and tenofovir DF. —

. There are no significant changes after storage in an — (except for a small increase in — from — or in the —

The stability of this formulation is also supported by the stability of the similar approved formulations for Truvada tablets and Sustiva tablets. The major stability trend seen for the individual formulations is the formation of tenofovir DF degradants, specifically — — and — total degradants. The expiration dating period for Truvada tablets is 24 months on storage at 25°C. Comparison of the rate of degradation of Truvada and — tablets over — at 40°C/75% RH shows that the rates of formation of — . and total degradants are similar.

For these reasons a 24 month expiration dating period with the following storage statement "Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F)" is acceptable.

Only the desiccant canister from — is used. However, it would be expected that the — is equally effective.

Stability testing protocols are provided. The first commercial batch of tablets in the alternate trade dress for export will be placed on stability at 30°C/65% RH.

The package insert is acceptable from a CMC point of view. The package insert contains the warnings "Keep container tightly closed" and "Dispense only in original container" in consideration of the moisture sensitivity of the product as does the container label (see above).

A categorical exclusion from the requirements to prepare an Environmental Assessment is requested.

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

— tablets are combination tablets containing efavirenz a non-nucleoside reverse transcriptase inhibitor and tenofovir disoproxil fumarate and emtricitabine, both nucleoside reverse transcriptase antagonists. — . is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The tablets contain 600 mg efavirenz, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate. The recommended dose is one tablet once daily taken orally on an empty stomach. The tablets are supplied in HDPE bottles containing 30 tablets and a silica gel desiccant. The storage recommendation is "Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]." The expiration dating period is 24 months. ———

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for efavirenz drug substance are described in approved NDAs 20-972 for Sustiva (efavirenz) Capsules and 21-360 for Sustiva (efavirenz) Tablets. The chemistry, manufacturing, and controls for tenofovir disoproxil fumarate drug substance are described in approved NDAs 21-356 for Viread (tenofovir disoproxil fumarate) Tablets and 21-752 for Truvada (emtricitabine/ tenofovir disoproxil fumarate) Tablets. The chemistry, manufacturing, and controls for emtricitabine drug substance are described in approved NDAs 21-500 for Emtriva (emtricitabine) capsules and 21-752 for Truvada (emtricitabine/ tenofovir disoproxil fumarate) Tablets. The composition, manufacturing process, and specifications for the tablets are appropriate and the expiration dating period of 24 months when stored at 25°Cis 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

Norman R. Schmuff, Ph.D. {Signed Electronically in DFS}

C. CC Block

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94 Page(s) Withheld

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

_ § 552(b)(5) Deliberative Process

_ § 552(b)(4) Draft Labeling

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
5/9/2006 09:29:05 AM
CHEMIST

Norman Schmuff
5/9/2006 10:49:13 AM
CHEMIST