CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-652

CHEMISTRY REVIEW(S)

NDA #21-652

EPZICOM™
(abacavir sulfate and lamivudine)
Tablets

GlaxoSmithKline

Rao Kambhampati, Ph.D.
Division of Antiviral Drug Products
HFD-530

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Chemistry Review Data Sheet

1. NDA# **21-652**

2. REVIEW #: 1

3. REVIEW DATE: 8/2/2004

4. REVIEWER: Rao V. Kambhampati, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	7/Oct/2003
Amendment (BC)	21/Nov/2003
Amendment (BZ)	19/Apr/2004
Amendment (BC)	18/Jun/2004
Amendment (BL)	9/Jul/2004

7. NAME & ADDRESS OF APPLICANT:

Name:	SmithKline Beecham d/b/a GlaxoSmithKline
Address:	One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101
Representative:	Martha Anne A. Moore, R.Ph. Director Antiviral/Antibacterial Regulatory Affairs
Telephone:	919-483-9347

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: EPZICOM™
b) Non-Proprietary Name (USAN): Abacavir sulfate and lamivudine
c) Code Name/#: 1592U89 and GR 109714X

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL CATEGORY: Antiviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine per tablet

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:

Abacavir Sulfate:

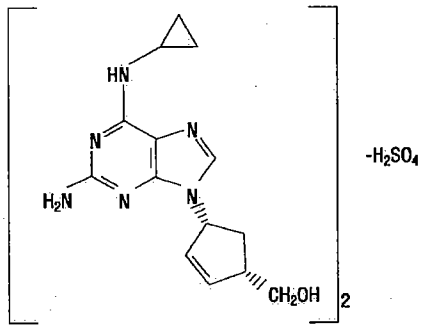
Chemical Name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1)

CAS Reg. No.: 188062-50-2

Molecular Formula: $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$

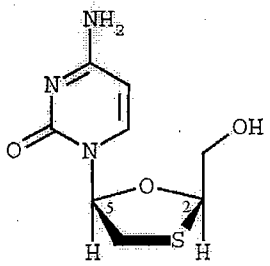
Molecular Weight: 670.74

Structural Formula:



Lamivudine:

Chemical Name: (-) 2',3'-dideoxy-3'-thiacytidine
CAS Reg. No.: 134678-17-4
Molecular Formula: $C_8H_{11}N_3O_3S$
Molecular Weight: 229.26
Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COD E[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	IV			1	Adequate	4/28/02	Acceptable
	III			1	Adequate	4/27/99	Acceptable
	III			1	Adequate	2/22/00	Acceptable
	III			4	N/A	N/A	Acceptable

Chemistry Review Data Sheet

	III		1	Adequate	8/30/01	Acceptable

[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
IND	45,331	Abacavir sulfate Tablets and Oral Solution
NDA	20-977	Abacavir sulfate Tablets
NDA	20-978	Abacavir sulfate Oral Solution
IND	37,158	Lamivudine
NDA	20-564	Lamivudine
NDA	20-596	Lamivudine
NDA	21-205	Trizivir Tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	11/24/03	J.D. Ambrogio (HFD-322), DMPQ, OC
Trademark Review	Acceptable	8/2/04	DMETS (HFD-420), ODS
EA	Acceptable (Categorical Exclusion)	7/27/04	Rao Kambhampati, Ph.D. (HFD-530)
Biopharm for Dissolution Method including acceptance criteria	Acceptable	6/7/04	Jenny H. Zheng, Ph.D. (HFD-530)
Methods Validation	Pending	7/27/04	Philadelphia District Laboratory (HFA-160)

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The Chemistry Review for NDA 21-652

The Executive Summary

I. Recommendations

- **A. Recommendation and Conclusion on Approvability**
  From the chemistry, manufacturing and controls (CMC) standpoint, the NDA #21-652 is recommended for approval.

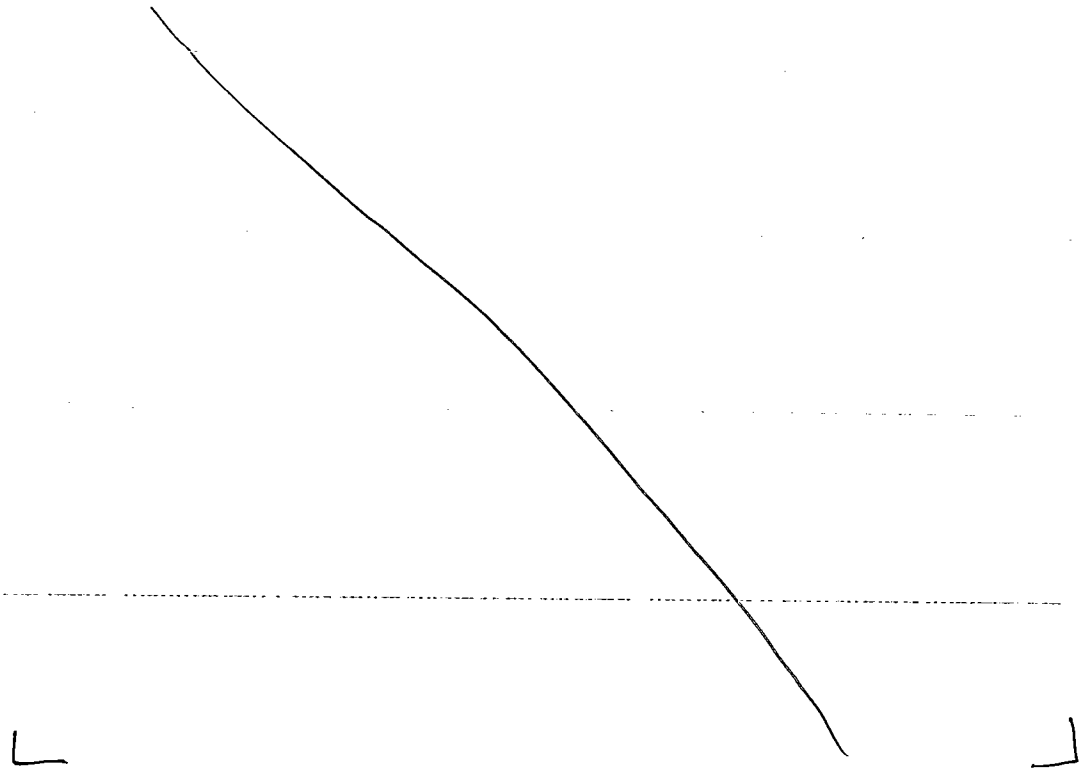
- **B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approval**
  N/A

II. Summary of Chemistry Assessments

- **A. Description of the Drug Substance(s) and Drug Product(s)**
  The Applicant intends to seek approval of the FDA for EPZICOM™ (abacavir sulfate and lamivudine) Tablets [initial NDA was submitted with the following name: Epivir/Ziagen (lamivudine and abacavir sulfate) Tablets] to be used in combination therapy for the treatment of patients with HIV infection. The Epzicom tablet is a fixed dose combination product of 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine. The tablets are packaged in bottles of 30 counts.

  All information regarding the chemistry, manufacturing and controls for the drug substances, abacavir sulfate and lamivudine were cross-referenced to the applicant's approved NDA 20-977 for Ziagen® (abacavir sulfate) Tablets and approved NDA 20-564 for Epivir® (lamivudine) Tablets, respectively, and all amendments and supplements thereto.

  The drug product is an oral tablet and is orange, film-coated, modified-capsule shaped (approximately 20.3 mm x 8.9 mm), and debossed with "GS FC2" on one side with no markings on the reverse side. The total weight of the tablet is approximately 1416 mg. The components and composition of the tablet core include abacavir sulfate [redacted] equivalent to 600 mg of abacavir), lamivudine (300 mg), microcrystalline cellulose ([redacted], sodium starch glycolate ([redacted] and magnesium stearate [redacted] and the film-coat include Opadry® Orange YS-1-13065-A [redacted]. The tablets are manufactured at Glaxo Operations UK Limited, Ware, UK. The tablet manufacturing process consists of [redacted]



Tablets and predict a shelf-life of greater than 36 months at 30°C/60%RH. In addition, data were provided for one batch of tablets that was stored for 6 months at 50°C with no significant changes from the initial time point. [redacted] (long-term and accelerated) supportive stability data were provided for one batch of tablets manufactured on a production scale at GSK, Ware, UK, using abacavir sulfate drug substance sourced from GSK, Cork, Ireland facility. The results are similar to those of the primary batches. The proposed expiration dating period of 36 months when stored at 25°C (77°C) is acceptable.

- **B. Description of How the Drug Product is Intended to be Used**
  Epzicom in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection. The recommended oral dose is one tablet daily. The tablets are packaged in . [redacted] bottles of 30 tablet count. The bottles are recommended to be stored at 25°C (77°F); excursions are permitted to 15° to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. On the basis of the stability data and statistical analysis of the data, the proposed expiration dating period of 36 months at 25°C (77°F) is acceptable.

- **C. Basis for Approvability or Not-Approval Recommendation**
  The original NDA submission and amendments there to provided adequate information on the chemistry, manufacturing, and controls for the production of abacavir sulfate-lamivudine tablets.

The applicant currently uses abacavir sulfate and lamivudine drug substances either alone or in combination for manufacturing of the following FDA approved drug products: Ziagen, Trizivir, Epivir, and Combivir. The CMC information for the drug substances was cross referenced to the approved NDAs and supplements there to. The manufacturing and packaging processes and in-process controls used for the drug product are acceptable. Adequate batch analysis data were provided for the drug product. The specification for the drug product included adequate tests and the proposed acceptance criteria are acceptable. The real-time ——— long-term stability data were provided for two commercial scale batches and one pilot scale batch and they demonstrated that the tablets are stable during this period. Statistical analysis of the data projected a stability period of ——— s. Based on the long-term real time data and statistical analysis of the data, the proposed expiration dating period of 36 months is acceptable when tablets are stored at 25°C.

The trade name, Epzicom, was found to be acceptable by the DMETS (HFD-420), DDMAC, and DAVDP (HFD-530). The established names for the drug substances, abacavir sulfate and lamivudine, are same as the USAN names. Some changes were recommended to the package insert, medication guide, and bottle and carton labels and those changes will be incorporated in the final printed documents by the Applicant.

The manufacturing, packaging, and release testing facility and the stability testing facility for tablets were found to be acceptable by DMPQ (HFD-324). The dissolution method including the acceptance criteria is acceptable from the CMC and from the biopharm perspective (Jenny H. Zheng, Ph.D.). The analytical methods validation is pending. The Applicant's request for an exemption from the EA requirement under categorical exclusion is acceptable.

III. Administrative

- **A. Reviewer's Signature**

  Signed electronically in DFS by Rao Kambhampati, Ph.D., Senior Regulatory Review Scientist

- **B. Endorsement Block**

  Signed electronically in DFS by Stephen P. Miller, Ph.D., Chemistry Team Leader

- **C. CC Block**cc:

Org. NDA 21-652	HFD-530/Chem Reviewer/RKambhampati
HFD-530/Division File	HFD-530/Chem Team Leader/SMiller
HFD-830/DD/DLin	HFD-530/PM/TSinha

52 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 1 of 1

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

/s/

Rao Kambhampati
8/2/04 02:11:25 PM
CHEMIST
Recommended for approval.
Please sign off and file.

Stephen Paul Miller
8/2/04 02:36:05 PM
CHEMIST