

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-205

**CHEMISTRY REVIEW(S)**

**REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROLS  
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)**

**1. CHEMISTRY REVIEW #:** 1

**2. NDA #:** 21-205

**3. NAME & ADDRESS OF APPLICANT:**

Glaxo Wellcome Inc.  
Five Moore Drive  
Research Triangle Park, NC 27709

**4. SUPPLEMENT(S):** N/A

**5. PROPRIETARY NAME:** Trizivir™

**6. NONPROPRIETARY NAME:** Abacavir sulfate, lamivudine, and zidovudine

**7. CODE NAME:** ABC + 3TC + ZDV

**8. CHEM TYPE/SUBMISSION PRIORITY:** 4 P

**9. SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

**10. PREVIOUS DOUMENTS**

**DOCUMENT DATE**

N/A

N/A

**11. SUBMISSION(S) REVIEWED**

**DOCUMENT DATE**

CMC Pre-NDA Submission

11-3-99

Original

12-16-99

Amendment BC

3-8-2000

Amendment BL

3-17-2000

Amendment BC

3-27-2000

Amendment BL

5-11-2000

**12. PHARMACOLOGICAL CATEGORY:**

Antiviral

**13. Rx or OTC:** Rx

**14. DOSAGE FORM:** Capsule-shaped, film-coated, tablet.

**15. STRENGTH/POTENCY:** Each tablet contains 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine.

**16. ROUTE OF ADMINISTRATION:** Oral

**17. SPOTS:**  No  Yes

**18. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT:**

a) Abacavir sulfate:

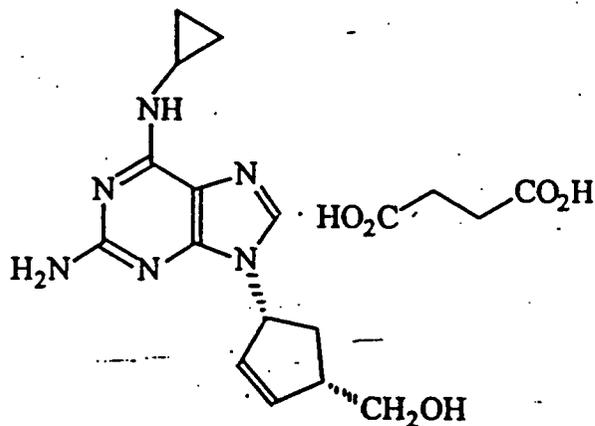
Chemical Name: [(1S,4R)-4-(2-amino-6-(cyclopropylamino)-9H-purin-9-

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## yl)-2-cyclopentene-1-methanol succinate

Structural Formula:

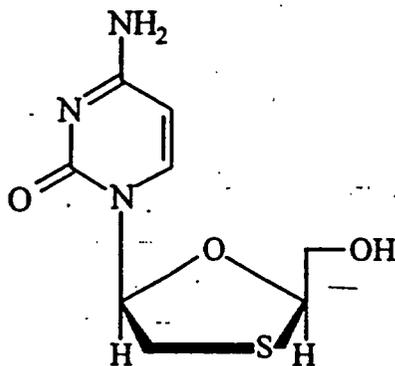
Molecular Formula: C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>O · C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>

Molecular Weight: 404.43

b) Lamivudine:

Chemical Name: (-) 2',3'-dideoxy-3'-thiacytidine

Structural Formula:

Molecular Formula: C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S

Molecular Weight: 229.30

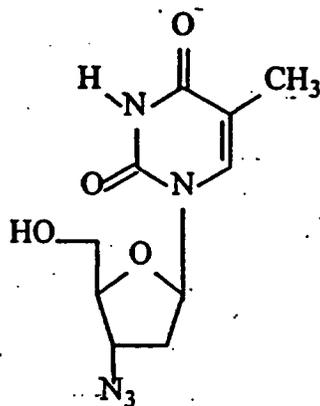
c) Zidovudine:

Chemical Name: 3'-Azido-3'-deoxythymidine

Structural Formula:

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Molecular Formula: C<sub>10</sub>H<sub>13</sub>N<sub>5</sub>O<sub>4</sub>

Molecular Weight: 267.24

**19. RELATED/SUPPORTING DOCUMENTS:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	_____	Abacavir sulfate Tablets and Oral Solution
NDA	20-977	Abacavir sulfate Tablets
NDA	20-978	Abacavir sulfate Oral Solution
IND	_____	Lamivudine
NDA	20-564	Lamivudine
NDA	20-596	Lamivudine
IND	_____	Zidovudine
NDA	19-655	Zidovudine
NDA	20-518	Zidovudine

DMF #	TYPE	HOLDER	ITEM REF	CODE	STATUS	DATE REVIEW COMPLETED	COMMENT
_____	IV	_____	_____	1	Adequate	11/24/99	Acceptable
_____	III	_____	_____	1	Adequate	11/12/99	Acceptable
_____	III	_____	_____	1	Adequate	12/13/99	Acceptable
_____	III	_____	_____	1	Adequate	4/27/99	Acceptable
_____	III	_____	_____	1	Adequate	2/22/00	Acceptable
_____	III	_____	_____	1	Adequate	2/29/00	Acceptable

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	III		manufacturer	1	Adequate	2/4/00	Acceptable
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<sup>1</sup> DMF Reviewed

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

**20. STATUS OF CONSULTS AND OTHER REVIEWS**

ITEM	RECOMMENDATION	a.	REVIEWER'S NAME
Microbiology	N/A	N/A	N/A
Inspection	Acceptable	Establishment Inspection	Melissa Egas (HFD-322)
Methods Validation	Pending	Analytical Methods Validation	Philadelphia D.O.
Biometrics	N/A	N/A	N/A
Biopharmaceutics	N/A	N/A	N/A
Trademark and labels	Acceptable		Jerry Phillips, R.Ph., OPDRA (HFD-400)

**21. REMARKS/COMMENTS:**

The Applicant submitted this NDA for the approval of Trizivir™ tablets containing a mixture of the following three drug substances as active ingredients, abacavir sulfate, lamivudine, and zidovudine for the treatment of HIV infection in adults and adolescents. The Trizivir™ (abacavir sulfate, lamivudine, and zidovudine) tablets are considered as a new solid oral dosage form containing a new formulation. Previously, for the treatment of HIV infection in humans, the FDA approved drug products (namely Ziagen®, Epivir®, and Retrovir®) containing one of the three active ingredients that are present in Trizivir as well as a drug product (Combivir®) containing two of the three active ingredients (lamivudine and zidovudine) present in Trizivir tablets. This is the first NDA submission to the FDA for a drug product that contains a mixture of three anti-HIV drug substances that are also reverse transcriptase inhibitors. The Trizivir™ tablets are capsule-shaped, blue-green in color, film-coated, and engraved with "GX LL1" on one side and no marking on the reverse side. The recommended dose of Trizivir for adults and adolescents (40 kg or above) is 1 tablet twice daily. The tablets are packaged into either bottles containing 60 tablets

**Drug Substance: Satisfactory**

All three drug substances that are needed for the manufacturing of Trizivir™ tablets obtained from the same FDA approved commercial manufacturing sites that supply the drug substances for the manufacture of the individual drug products; Ziagen, Epivir, and Retrovir, and the combination drug product, Combivir. The Applicant provided cross-references to the Applicant's appropriate NDAs and amendments for information regarding the CMC of these drug substances. Copies of the current specifications for all three drug substances were provided in this NDA submission.

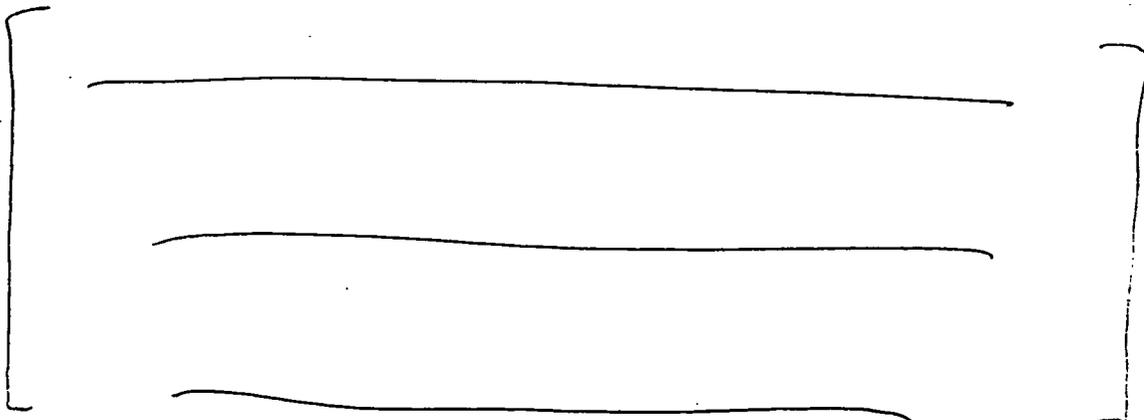
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Drug Product: Satisfactory

The components and composition of each Trizivir™ tablet (core wt. = 1350 mg) consists of abacavir sulfate ( \_\_\_\_\_ equivalent to 300 mg of abacavir), lamivudine (150 mg), and zidovudine USP (300 mg) as active ingredients and microcrystalline cellulose \_\_\_\_\_ mg), sodium starch glycolate \_\_\_\_\_ mg), and magnesium stearate \_\_\_\_\_ mg) as excipients and Opadry Green® 03B11434 \_\_\_\_\_ mg) as the film-coat which is made of FD&C Blue No. 2, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and yellow iron oxide.

Representative batch formulas for a \_\_\_\_\_ batch of the core tablets and a \_\_\_\_\_ batch of the film-coating suspension were provided. All excipients used are of USP or NF grade except Opadry Green 03B11434 for which the Applicant provided satisfactory acceptance specifications which included appearance / \_\_\_\_\_, identity by \_\_\_\_\_ residue on ignition \_\_\_\_\_, and heavy metals / \_\_\_\_\_ ppm). A LOA was provided from the \_\_\_\_\_ for the cross-reference of DMF \_\_\_\_\_ for the CMC information.



The in-process controls included tablet weight, hardness, thickness, and friability and they are adequate.

The specifications for the container/closure components (HDPE bottle, child-resistant closure, \_\_\_\_\_ forming material, \_\_\_\_\_, included identity by \_\_\_\_\_ visual inspection, and dimensional inspection. The bulk tablets are packaged in clear \_\_\_\_\_

\_\_\_\_\_ were provided for HDPE bottle, child-resistant closure, and a single blister cavity of the NDA stability lot. Upon comment, the Applicant provided \_\_\_\_\_

Two pilot-scale batches ( \_\_\_\_\_ kg) and one production-scale batch ( \_\_\_\_\_ kg) of the tablets were manufactured using equipment of the same design and operating principle intended for commercial manufacturing of the product. Satisfactory batch analysis data were provided for these batches and the data demonstrated that the manufacturing process consistently produces a product that meets the proposed regulatory specifications.

The tablets are packaged into either \_\_\_\_\_ HDPE bottles of 60-count, \_\_\_\_\_

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The proposed sampling plan for the batch release testing is adequate. The proposed specifications included appearance, identification of abacavir, lamivudine, and zidovudine by HPLC, assay for abacavir, lamivudine, and zidovudine contents by HPLC, drug-related impurities by HPLC, dissolution of abacavir, lamivudine, and zidovudine by UV, and abacavir, lamivudine, and zidovudine content uniformity by UV. The drug-related impurities testing includes limits for \_\_\_\_\_, any unspecified impurity, total abacavir-related impurities, total lamivudine-related impurities, and total zidovudine-related impurities. A description was provided for all the analytical methods used for testing and the method validation data were provided for the HPLC method used for the identity, assay, and drug-related impurities and for UV methods used for dissolution and content uniformity. Upon comment, the Applicant made the following changes to the proposed specifications: a) a second identity method that involves the identification of abacavir, lamivudine, and zidovudine by \_\_\_\_\_ method was added, b) the limit for \_\_\_\_\_ impurity was tightened from NMT \_\_\_\_\_ to NMT \_\_\_\_\_, c) moisture content testing was added to the NDA stability lots test protocol and, a justification was provided for not including the moisture content in the lot release specifications and in the commercial lot stability test protocol, and d) a detailed justification was provided for the exclusion of microbial limits test. The amended specifications are adequate and they are expected to control the identity, assay, quality, and purity of the tablets.

The stability data were provided for two pilot scale batches and one production scale batch that were packaged in HDPE bottles and \_\_\_\_\_. All three batches were made at the site intended for commercial manufacture, using equipment of the same design and operating principle. The studies indicated that there was no significant degradation when the samples were stored for \_\_\_\_\_ (accelerated condition). In addition, data were provided for a production-scale batch that was stored for \_\_\_\_\_ conditions. This data also indicated that there was no significant degradation. A \_\_\_\_\_ Test Protocol for the NDA stability batches, a \_\_\_\_\_ Test Protocol for the first two commercial batches and a \_\_\_\_\_ test protocol for the annual stability batches were provided. Based on the provided stability data and the statistical analysis, the Applicant proposed an expiration period of 24 months when the Trizivir tablet packages are stored at 25°C [excursions permitted to 15-30°C (59-86°F), see USP Controlled Room Temperature]. Based on the available stability data and statistical analysis, the Applicant's proposed expiration period of 24 months is acceptable.

**ENVIRONMENTAL ASSESSMENT: *Satisfactory***

The Applicant's justification for exemption from the environmental assessment requirement is acceptable.

**METHODS VALIDATION: *Pending***

The analytical methods validation by the FDA district laboratory is pending

**LABELING: *Satisfactory***

The CMC comments that are related to the labels on bottle and the cartons used for packaging of commercial blisters and physician sample blisters were communicated to the Applicant through the Project Manager (HFD-530). The revised labels were reviewed and they are acceptable. The trademark TRIZIVIR™ for tablets containing abacavir sulfate, lamivudine, and zidovudine was reviewed by OPDRA and it was found to be acceptable.

**ESTABLISHMENT INSPECTION: *Satisfactory***

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The manufacturing, packaging, labeling, and quality control of Trizivir tablets are conducted at Glaxo Wellcome Inc, Zebulon, North Carolina and the stability testing of NDA registration batches were being conducted at Glaxo Wellcome Inc, Research Triangle Park, North Carolina. However, the on-going stability studies of the commercial batches will be conducted at the Zebulon site. All facilities were clearly identified. All establishments that are involved in the manufacturing, packaging, quality control, and stability testing of tablets and the drug substances' manufacturing facilities were found to be acceptable and an Overall Acceptable Recommendation was issued on 6/2/2000 by Melissa Egas of HFD-324 (DMPQ, OC).

**22. CONCLUSIONS & RECOMMENDATIONS:**

From the CMC stand point the NDA 21-205 for Trizivir™ (abacavir sulfate, lamivudine, and zidovudine) tablets is approved. An expiration dating period of 24 months is recommended for Trizivir™ tablets that are packaged in bottles of 60 count or in unit dose blister packs and stored at 25°C (77° F). In the NDA Action Letter, a statement should be included indicating that the analytical methods validation by the FDA District Laboratory is pending.

**23. REVIEWER**

*IS*  
 Rao V. Kambhampati, Ph.D.  
 Senior Regulatory Review Scientist

**DATE COMPLETED**

*IS*  
 6/2/2000  
 Final 7/20/2000

**Concurrence:**

HFD-530/Chem. TL/SMiller

*IS* 7/21/00

**cc:**

Orig. NDA #21-205  
 HFD-530/Chem TL/SMiller  
 HFD-530/MO/JMartin  
 HFD-530/Micro/LMishra  
 HFD-530/Biopharm/PRajagopalan

HFD-530/Chem/RKambhampati  
 HFD-830/Dir/CChen  
 HFD-530/PM/MTruffa  
 HFD-530/Pharm/PVerma

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**REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROLS  
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)**

**1. CHEMISTRY REVIEW #:** 2

**2. NDA #:** 21-205 (Resubmission)

**3. NAME & ADDRESS OF APPLICANT:**

Glaxo Wellcome Inc.  
Five Moore Drive  
Research Triangle Park, NC 27709

**4. SUPPLEMENT(S):** N/A

**5. PROPRIETARY NAME:** Trizivir™

**6. NONPROPRIETARY NAME:** Abacavir sulfate, lamivudine, and zidovudine

**7. CODE NAME:** ABC + 3TC + ZDV

**8. CHEM TYPE/SUBMISSION PRIORITY:** N/A (Resubmission)

**9. SUPPLEMENT(S) PROVIDE(S) FOR:** N/A

**10. PREVIOUS DOUMENTS**

**DOCUMENT DATE**

CMC Pre-NDA Submission

11-3-99

Original

12-16-99

Amendment BC

3-8-2000

Amendment BL

3-17-2000

Amendment BC

3-27-2000

Amendment BL

5-11-2000

**11. SUBMISSION(S) REVIEWED**

**DOCUMENT DATE**

NDA Amendment AZ

9-13-2000

**12. PHARMACOLOGICAL CATEGORY:**

Antiviral

**13. Rx or OTC:** Rx

**14. DOSAGE FORM:** Capsule-shaped, film-coated, tablet.

**15. STRENGTH/POTENCY:** Each tablet contains 300 mg of abacavir as abacavir sulfate, 150 mg of lamivudine, and 300 mg of zidovudine.

**16. ROUTE OF ADMINISTRATION:** Oral

**17. SPOTS:**  No  Yes

**18. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
MOLECULAR WEIGHT:**

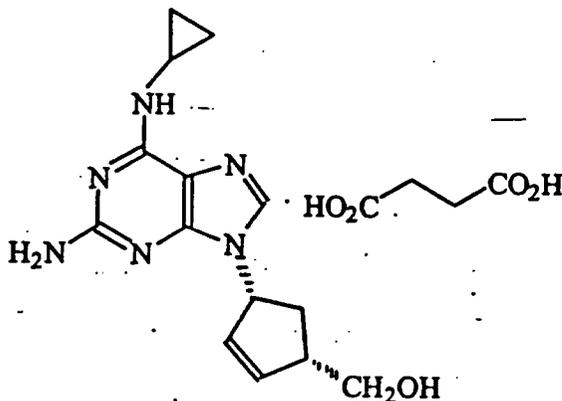
a) Abacavir sulfate:

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Chemical Name: [(1S,4R)-4-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-methanol succinate

Structural Formula:

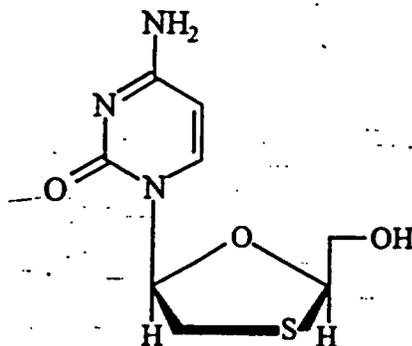


Molecular Formula: C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>O · C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>  
Molecular Weight: 404.43

b) Lamivudine:

Chemical Name: (-) 2',3'-dideoxy-3'-thiacytidine

Structural Formula:



Molecular Formula: C<sub>8</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S  
Molecular Weight: 229.30

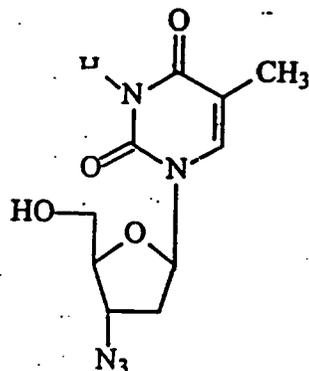
c) Zidovudine:

Chemical Name: 3'-Azido-3'-deoxythymidine

Structural Formula: \_\_\_\_\_

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Molecular Formula:  $C_{10}H_{13}N_5O_4$ 

Molecular Weight: 267.24

**19. RELATED/SUPPORTING DOCUMENTS:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Chemistry Review #1	21-205	CMC review of initial submission and amendments submitted prior to 6/2/00.
IND		Abacavir sulfate Tablets and Oral Solution
NDA	20-977	Abacavir sulfate Tablets
NDA	20-978	Abacavir sulfate Oral Solution
IND		Lamivudine
NDA	20-564	Lamivudine
NDA	20-596	Lamivudine
IND		Zidovudine
NDA	19-655	Zidovudine
NDA	20-518	Zidovudine

DMF #	TYPE	HOLDER	ITEM REF	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
—	IV	—	—	1	Adequate	11/24/99	Acceptable
—	III	—	—	1	Adequate	11/12/99	Acceptable
—	III	—	—	1	Adequate	12/13/99	Acceptable
—	III	—	—	1	Adequate	4/27/99	Acceptable
—	III	—	—	1	Adequate	2/22/00	Acceptable

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	III			1	Adequate	2/29/00	Acceptable
	III			1	Adequate	2/4/00	Acceptable

<sup>1</sup> DMF Reviewed

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

**20. STATUS OF CONSULTS AND OTHER REVIEWS:**

ITEM	RECOMMENDATION	a.	REVIEWER'S NAME
Microbiology	N/A	N/A	N/A
Inspection	Acceptable	Establishment Inspection	Melissa Egas (HFD-322)
Methods Validation	Pending	Analytical Methods Validation	Philadelphia D.O.
Biometrics	N/A	N/A	N/A
Biopharmaceutics	N/A	N/A	N/A
Trademark and Labels	Acceptable		Jerry Phillips, R.Ph., OPDRA (HFD-400)

**21. REMARKS/COMMENTS:**

The DAVDP issued an approvable letter to Glaxo Wellcome on June 9, 2000 in response to their NDA #21-205 (Trizivir tablets) which was initially submitted on December 16, 1999. As according to the 21 CFR 314.110, in this resubmission, the Applicant provided a complete response to the June 9, 2000 approvable letter. Please see the Chemistry Review #1 (7/21/00) for a detailed review of the initial NDA submission and amendments that were submitted until 6/2/00.

This resubmission amendment (9/13/00) contained the following documents that contain chemistry related information: a) revised sample labels for the bottle, commercial and sample blister printmats, and cartons for bottle and blisters, b) revised package insert, c) revised medication guide for Ziagen and Trizivir, and d) revised warning card for Ziagen and Trizivir. These revised documents contained all the CMC changes that were agreed upon by the Applicant. See Appendix 1 for copies of sample labels.

**22. CONCLUSIONS & RECOMMENDATIONS:**

The resubmission amendment (9/13/00) containing the revised labels, package insert,

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medication guide, and warning card are acceptable. From the CMC stand point, the NDA #21-205 for Trizivir™ (abacavir sulfate, lamivudine, and zidovudine) tablets is recommended for approval. An expiration dating period of 24 months is recommended for Trizivir™ tablets that are packaged in bottles of 60 count or in unit dose blister packs and stored at 25°C (77° F). In the NDA Action Letter, a statement should be included indicating that the analytical methods validation by the FDA District Laboratory is pending.

23. REVIEWER \_\_\_\_\_ DATE COMPLETED \_\_\_\_\_  
Rao V. Kambhampati, Ph.D.  
Senior Regulatory Review Scientist

Concurrence:  
HFD-530/Chem. TL/SMiller

cc:

Orig. NDA #21-205  
HFD-530/Chem TL/SMiller  
HFD-530/MO/JMartin  
HFD-530/Micro/LMishra  
HFD-530/Biopharm/

HFD-530/Chem/RKambhampati  
HFD-830/Dir/CChen  
HFD-530/PM/MTruffa  
HFD-530/Pharm/PVerma

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/s/

-----  
Rao Kambhampati  
11/1/00 05:52:38 PM  
CHEMIST

Recommended for Approval.  
Please sign off and file.

Stephen Paul Miller  
11/2/00 09:20:31 AM  
CHEMIST

"Last Signature Comment"

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