CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-478

CHEMISTRY REVIEW(S)

NDA 21-478

ZOVIRAX® (acyclovir) Cream 5%

GlaxoSmithKline Inc.

Zi-Qiang Gu, Ph.D.
Division of Antiviral Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA # **21-478**

2. REVIEW # **1**

3. REVIEW DATE: **December 30, 2002**

4. REVIEWER: **Zi-Qiang Gu, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 21-122	4/1/1999

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	3/15/2002

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline
Address:	Five Moore Drive, Research Triangle Park, NC 27709
Representative:	Ms. Grace Pagano, Assistant Director
Telephone:	919-483-1382

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: **Zovirax® Cream 5%**
b) Non-Proprietary Name (USAN): **Acycovir**
c) Code Name/# (ONDC only): **N/A**
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: **Cream**

12. STRENGTH/POTENCY: **5%**

13. ROUTE OF ADMINISTRATION: **Topical**

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

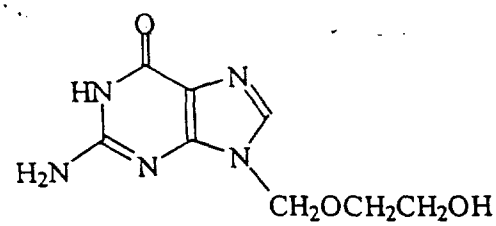
___X__Not a SPOTS product

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

2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-6H-purine-6-one

Molecular formula: $C_8H_{11}N_5O_3$

Relative molecular mass: —



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III	—	—	3	Adequate	3/27/2001 9/17/1999 6/23/1993	
	III	—	—	4	N/A	N/A	

[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
NDA	18-604	Zovirax Ointment 5%
NDA	21-122	Zovirax Cream 5%

18. STATUS:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical	Approvable		T. Wu
Biometrics	Approvable		F. Smith
Pharm/Tox	Approvable		A. Bigger
Microbiology	Approvable		N. Biswal
Biopharm	Approvable		R. Kumi
Proprietary Name	Acceptable	9/24/99	CDER Labeling and Nomenclature Committee (LNC)
Methods Validation	Pending		
EA	Exclusion Acceptable		Z.Gu
EES	Acceptable	7/25/02	S. Adams (HFD-324)

The Chemistry Review for NDA 21-478

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information of acyclovir drug substance in this NDA remains unchanged from that provided in the NDA 18-604 for Zovirax Ointment, 5%. The CMC data for the drug product, Zovirax Cream, 5%, are adequate. Therefore, the NDA is recommended for approval from the chemistry, manufacturing and controls perspective.

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

N/A

II. Summary of Chemistry Assessments

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

The active pharmaceutical ingredient (API), acyclovir, is a synthetic nucleoside analogue with antiviral activity against herpesviruses. Complete information on the synthesis and manufacturing controls for the drug substance is contained within the approved application for Zovirax® (acyclovir) Oinment, 5% (NDA 18-604). As agreed at the July 2, 1997 pre-NDA meeting, all manufacturing and controls information for the drug substance is cross referenced to NDA 18-604.

The drug product, Zovirax®, contains 5% w/w acyclovir dispersed into a cream base, is proposed for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older). Zovirax® Cream contains acyclovir plus excipients commonly used in topical preparation (e.g. propylene glycol, white petrolatum, cetostearyl alcohol, poloxamer 407, sodium lauryl sulfate, etc). For the commercial market, Zovirax® Cream will be supplied in 2-gram collapsible aluminum tubes and closed with a ——— screw cap. For the physician sample package, it will be supplied as a 0.8-gram tube ——— tube), which is the same type and product contact materials as the tube proposed for the trade pack.

The manufacturing process of the drug product includes the [redacted] t and filling into tubes and crimp. The regulatory specification for Zovirax® Cream includes description, identification, pH, viscosity, assay, related substances, particle size of acyclovir, minimum fill, and microbial limit.

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

Zovirax® Cream should be applied five times per day for 4 days for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents. A single 2-gram tube would be enough supply for a 4-day treatment.

The primary stability data generated on three commercial scale production batches indicate that the drug product is stable at 30°C/60% for [redacted] at 37°C/Ambient RH for [redacted] and at 5°C/37°C cycling for [redacted] No stability problems and trends of degradation were observed in the stability study under these conditions. A shelf-life of 24 months is granted for Zovirax® Cream 5% when stored at the defined storage conditions 25°C with excursions permitted to 30°C (see USP Controlled Room Temperature).

C. Basis for Approvability or Not-Approval Recommendation

Upon request, tests such as homogeneity, propylene glycol content, and other impurities (each not more than 0.1%) are added in the drug product specification. As amended, all methods and acceptance criteria were found acceptable for the drug product. However, the methods and their validation have to be evaluated in FDA laboratories. The NDA submission and amendment ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Zovirax® Cream 5%.

An overall recommendation of acceptable cGMP for the drug product manufacturing site (including manufacturing, packaging, release test and stability test) was received from Office of Compliance on July 25, 2002.

The trade name was found acceptable by OPDRA and by the Division of Antiviral Drug Products. The labeling is being reviewed due to the anticipated action for approval for this NDA.

III. Administrative

A. Reviewer's Signature

Chemist:
Zi-Qiang Gu, Ph.D. ***{Signed electronically in DFS}***

B. Endorsement Block

Chemistry Team Leader:
Stephen P. Miller, Ph.D. {Signed electronically in DFS}

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

/s/

Zi-Qiang Gu
1/21/03 02:11:33 PM
CHEMIST

Chemistry review

Stephen Paul Miller
1/21/03 03:39:45 PM
CHEMIST