CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-487 /S-005

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

ORIGINAL

January 10, 2005

SLR-005-FA

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398
Tel. 919 483 2100
www.gsk.com

Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Boulevard
Rockville, MD 20850

Re: NDA 20-487/S-005; VALTREX® (valacyclovir hydrochloride) Caplets
Response to Approval Letter: FPL

Dear Dr. Birnkrant:

Please refer to our supplemental new drug application for VALTREX (valacyclovir hydrochloride) Caplets dated February 19, 2004 which provided for updating the PRECAUTIONS: Nursing Mothers subsection of the prescribing information regarding acyclovir concentrations in human breast milk following administration of VALTREX to nursing mothers. Please also refer to your approval letter dated December 3, 2004.

We are submitting the final printed labeling electronically in accordance with the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format –NDAs, January 1999*. Please see the Guide to Reviewers for detailed information about this electronic submission. The labeling is identical to the draft labeling submitted on November 11, 2004. A Word version of the insert is provided as a reviewer aid.

If you have any questions regarding this submission, please contact me at 919-483-6030. Thank you.

Sincerely,

Sherman N. Alfors
Director, Antiviral/Antibacterial
US Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Memorandum of Project Manager's Review: Final Printed Labeling

Date of Review: November 12, 2004

NDA Number: 20-487/S-005

Date of Submission: February 19, 2004

Applicant: GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Product Name: Valtrex® (valacyclovir hydrochloride) Caplets

Materials Reviewed: February 19, 2004 Final Printed Labeling (FPL) and November 11, 2004 FPL
Final Printed Labeling approved February 4, 2004 (NDA 20-550/SE1-019)

Background:

This Prior Approval Supplement Final Printed Labeling provides for the revision of the PRECAUTIONS: Nursing Mothers subsection of the labeling for this drug product. The proposed wording is based on data from a manuscript by Jeanne S. Sheffield, MD, et. al., of the University of Texas Southwestern Medical Center, printed in the American Journal of Obstetrics and Gynecology in January 2002. Results from this study reported serum and human breast milk concentrations, ratios of serum to milk at different time points, as well as acyclovir concentrations from infant urine following maternal administration of Valtrex®. On November 5, 2004, the Division recommended the inclusion of additional language. The applicant accepted the Division's recommendation and submitted revised labeling in the letter dated November 11, 2004. This labeling was compared to the labeling approved by the Division of Antiviral Drug Products on February 4, 2004.

Summary of Review

The PRECAUTIONS: Nursing Mothers subsection of the package insert was revised as follows. No changes were made to the PATIENT INFORMATION section of the labeling.

Nursing Mothers: Following oral administration of a 500-mg dose of VALTREX to 5 nursing mothers, peak acyclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 times (median 1.4) the corresponding maternal acyclovir serum concentrations. The acyclovir breast milk AUC ranged from 1.4 to 2.6 times (median 2.2) maternal serum AUC. A 500-mg maternal dosage of VALTREX twice daily would provide a nursing infant with an oral acyclovir dosage of approximately 0.6 mg/kg/day. This would result in less than 2 % of the exposure obtained after administration of a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir to the nursing infant. Unchanged valacyclovir was not detected in maternal serum, breast milk, or infant urine. ~~There is no experience with VALTREX. However, acyclovir concentrations~~

~~have been documented in breast milk in 2 women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day.~~ VALTREX should be administered to a nursing mother with caution and only when indicated.

An approval letter will be issued to the applicant.

_____

Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

Attachments: Comparison of November 11, 2004 Final Printed Labeling (SLR-005) and Final Printed Labeling approved February 4, 2004 (NDA 20-550/SE1-019).

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/s/

Nitin Patel
12/2/04 02:00:44 PM
CSO

Tony DeCicco
12/3/04 11:11:54 AM
CSO

November 11, 2004

GlaxoSmithKline
PO Box 13398
Five Moore Drive
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North Carolina 27709
Tel. 919 483 2100
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Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Boulevard
Rockville, MD 20850

SLR-005-BL

Re: NDA 20-487/S-005; VALTREX® (valacyclovir hydrochloride) Caplets
Response to FDA Request/Comment: Response to Labeling Comments Dated November 5, 2004

NDA SUPPL AMENDMENT

Dear Dr. Birnkrant:

Please reference our New Drug Application 20-487 for Valtrex (valacyclovir hydrochloride) Caplets for the treatment and suppression of herpes infections. The purpose of this correspondence to state our acceptance, without further revisions, of your labeling comments provided to us on November 5, 2004.

Please reference the following submissions and correspondences:

February 19, 2004	GSK submitted a prior approval labeling supplement to add information in the Precaution section of the labeling. The information added was based on an article by J. Sheffield, MD, "Acyclovir concentrations in human breast milk after valaciclovir administration," published in the American Journal of Obstetrics and Gynecology.
March 29, 2004	FDA assigned supplement number 005.
July 29, 2004	FDA requested a copy of the study protocol and pharmacokinetic data from individual patients.
September 7, 2004	GSK provided requested information.
November 5, 2004	FDA provided revised labeling with additional wording regarding exposure of acyclovir to infants.
November 11, 2004	GSK accepts the new wording without further revisions.

As stated above, we are in agreement with and accept the revised labeling provided on November 5, 2004. We are providing 'clean copy' labeling with this submission.

ORIGINAL

This submission is provided in electronic format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999.* Please see the attached Guide to Reviewer for complete details on the electronic submission. We are providing this submission in duplicate, with two desk copies to Nitin Patel, RPh, Regulatory Project Manager.

If you have any questions regarding this submission please contact me at (919) 483-6030. Thank you.

Sincerely,

Sherman N. Alfors
Director, Antiviral/Antibacterial
US Regulatory Affairs

Attachment: Valtrex Prescribing Information 'Clean Copy'

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On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 5, 2004

To: Sherman N. Alfors
Director, Antiviral/Antibacterial Regulatory Affairs
GlaxoSmithKline

From: Nitin Patel, R.Ph., Regulatory Project Manager, DAVDP

Through: Vikram Arya, Ph.D., Clinical Pharmacology Reviewer, DAVDP
Kellie S. Reynolds, Pharm.D., Clinical Pharmacology Team Leader, DAVDP
Kendall Marcus, M.D., Medical Team Leader, DAVDP

NDA: NDA 20-487/S-005

Drug: VALTREX® (valacyclovir hydrochloride) Caplets

Subject: Labeling recommendations regarding Prior Approval Labeling Supplement

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Please refer to your Prior Approval Labeling Supplement, dated February 19, 2004, which proposes revisions to the PRECAUTIONS: Nursing Mothers subsection of the labeling for Valtrex® Caplets. The review team recommends inclusion of the underlined text as provided below:

Nursing Mothers: Following oral administration of a 500-mg dose of VALTREX to 5 nursing mothers, peak acyclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 times (median 1.4) the corresponding maternal acyclovir serum concentrations. The acyclovir breast milk AUC ranged from 1.4 to 2.6 times (median 2.2) maternal serum AUC. A 500-mg maternal dosage of VALTREX twice daily would provide a nursing infant with an oral acyclovir dosage of approximately 0.6 mg/kg/day. This would result in less than 2 % of the exposure obtained after administration of a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir to the nursing infant. Unchanged valacyclovir was not detected in maternal serum, breast milk, or infant urine. VALTREX should be administered to a nursing mother with caution and only when indicated.

Please let us know if these changes are acceptable to you, by November 12, 2004.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Nitin Patel
11/9/04 04:59:14 PM
CSO

Kendall Marcus
11/10/04 08:21:55 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-487/S-005

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
Attention: Sherman N. Alfors
Director, Antiviral/Antibacterial
US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Dear Mr. Alfors:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	VALTREX® (valacyclovir hydrochloride) 500 mg Caplets
NDA Number:	20-487
Supplement number:	S-005
Date of supplement:	February 19, 2004
Date of receipt:	February 20, 2004

This supplemental application proposes to revise the PRECAUTIONS: Nursing Mothers subsection of the labeling for this drug product. The proposed wording is based on the results of a study which you have provided. Results from this study reported serum and human breast milk concentrations, ratios of serum to milk at different time points, as well as acyclovir concentrations from infant urine following maternal administration of Valtrex®.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 20, 2004 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Control Room, N115
9201 Corporate Blvd
Rockville, MD 20850

If you have any questions, call Nitin Patel, R.Ph., Regulatory Project Manager, at (301) 827-2335

Sincerely,

{See appended electronic signature page}

Anthony W. DeCicco, RPh
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Tony DeCicco
3/29/04 01:28:01 PM

February 19, 2004

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Boulevard
Rockville, MD 20850

NDA NO. 20-487 REF NO. 005
NDA SUPPL FOR SLR

Re: NDA 20-487/S-005; VALTREX® (valacyclovir hydrochloride) Caplets
Supplement: Prior Approval, Labeling; Pharmacokinetics (Human Breast Milk)

Dear Dr. Birnkrant:

Please reference our New Drug Application 20-487 for Valtrex (valacyclovir hydrochloride) Caplets for the treatment and suppression of herpes infections. The purpose of this supplement is to propose revisions to the **PRECAUTIONS: Nursing Mothers** subsection of the labeling for this drug product.

The proposed wording is based on data from the manuscript provided (Sheffield.pdf) by Jeanne S. Sheffield, MD, et. al., of the University of Texas Southwestern Medical Center at Dallas and printed in the American Journal of Obstetrics and Gynecology in January 2002. Results from this study reported serum and human breast milk concentrations, ratios of serum to milk at different time points, as well as acyclovir concentrations from infant urine following maternal administration of Valtrex. This study concludes that valacyclovir quickly converts to acyclovir and concentrates in breast milk. The amount of acyclovir in breast milk after valacyclovir administration is considerably less than that used in therapeutic dosing of neonates. Present wording in the **PRECAUTIONS: Nursing Mothers** subsection is based on administration of acyclovir.

Please note that no proposed changes have been made to the current wording in the '**Before taking VALTREX, tell your healthcare provider: if you are breastfeeding**' subsection of the PATIENT INFORMATION section of the labeling. We believe that the wording in this section correctly conveys the current knowledge of valacyclovir related to breastfeeding, without overly alarming patients. The dominant message is for patients to talk with their healthcare providers.

ORIGINAL

This submission is provided in electronic format according to *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999.* Please see the attached Guide to Reviewer for complete details on the electronic submission. We are providing clean and revised copies of the draft labeling in Word, as reviewer aids.

If you have any questions regarding this submission please contact me at (919) 483-6030. Thank you.

Sincerely,

Sherman N. Alfors
Director, Antiviral/Antibacterial
US Regulatory Affairs

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