CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-550/S-012

ADMINISTRATIVE DOCUMENTS

Time Sensitive Patent Information

Pursuant to 21 C.F.R. § 314.53
for

VALTREX® (valacyclovir hydrochloride) Caplets for Genital Herpes

Item 13 of Supplemental NDA 20-550

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: VALTREX®

Active Ingredient: valacyclovir hydrochloride

Strength(s): 500 mg

Dosage Form: caplet

U.S. Patent	Expiration Date	Type of Patent	Patent Owner	U.S. Agent
4,567,182	28 January 2003	Drug Product Composition/ Formulation	Co Pharma Corp. s.r.l. (licensed to Glaxo Wellcome Inc.)	Glaxo Wellcome Inc.
4,957,924	23 June 2009	Drug Product Composition/ Formulation Method of Use	Glaxo Wellcome Inc.	Glaxo Wellcome Inc.
5,879,706	19 January 2016	Composition/ Formulation Method of Use	Glaxo Wellcome Inc.	Glaxo Wellcome Inc.

The undersigned declares that U.S. Patent 4,567,182 covers the drug product formulation, and composition of VALTREX® (valacyclovir hydrochloride). This patent is licensed to Glaxo Wellcome Inc. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent 4,957,924 covers the drug product, formulation, composition and method of use of VALTREX® (valacyclovir hydrochloride). The expiration date, 23 June 2009, was extended 323 days from the original expiration date of 4 August 2008

1

pursuant to 35 U.S.C. §156. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent 5,879,706 covers the formulation, composition and method of use of VALTREX® (valacyclovir hydrochloride). This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Please address all communications to:

David J. Levy, Ph.D.
Patent Counsel
Glaxo Wellcome Inc.
Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-7656

Respectfully submitted,

Date: 26 July, 2000

David J. Levy, Ph.D.
Attorney for Applicant
Glaxo Wellcome Inc.

lam:i:\lsrv\VALTREX®\endopatinfo.doc

EXCLUSIVITY SUMMARY for NDA # 20-550 SUPPL # SE2-012

Trade Name Valtrex® Generic Name valacyclovir hydrochloride

Applicant Name Glaxo Smith Kline HFD- 530

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE2

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-550 _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # HS2A4004

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 HS2A4004 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 HS2A4004 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # ___HS2A4004_____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_X_/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

/

[S]
Signature of Prepared

1/16/01
Date

Title: Regulatory Project Manager

[S]
Signature of Office of Division Director

1/22/01
Date

cc:
Archival NDA
HFD-530/Division File
HFD-530/Young
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020550
Trade Name: VALTREX (VALACYCLOVIR HCL) CAPLETS
Generic Name: VALACYCLOVIR HCL
Supplement Number: 012 **Supplement Type**: SE2
Dosage Form:
Regulatory Action: OP **Action Date**: 8/31/00
COMIS Indication: TREATMENT OF RECURRENT GENITAL HERPES

Indication #1: Episodic treatment of recurrent genital herpes
Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
0	12 years	Waived	

Comments: Do not perceive a medical need for treatment of recurrent genital herpes in the pre-pubertal patient population.

12 years	16 years	Waived	

Comments: Data from the adult studies can be extrapolated for the adolescent population.

This page was last edited on 5/29/01

(S)
Signature

5/29/01
Date

NDA 20-550 VALTREX® (valacyclovir hydrochloride) Caplets

Supplemental New Drug Application for Short Course
Episodic Treatment of Recurrent Genital Herpes

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

2 AUG 2000

Charles E. Mueller
Head, North American Clinical Compliance
World Wide Compliance

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

CSO Labeling Review

Date of Review: May 14, 2001

NDA Number: 20-550

Product Name: Valtrex® (valacyclovir hydrochloride) Caplets

Sponsor: GlaxoSmithKline

Supplements: 010, 012, 013

Dates of Submission:			**Dates Received:**
	010	August 9, 1999	August 10, 1999
	012	August 30, 2000	August 31, 2000
	013	October 26, 2000	October 27, 2000

Materials Reviewed: (Dates Received)		
	009 & 011	January 21, 2000 (Final Printed Labeling)
	010	August 10, 1999 (SLR)
	012	August 31, 2000 (SLR)
	010	October 27, 2000 (Revised Labeling Supplement)
	013	October 27, 2000 (SLR)
	010	February 26, 2001 (Revised Labeling Supplement)
	010 & 012	March 5, 2001 (Revised Labeling Supplement)
	010 & 012	March 20, 2001 (Revised Labeling Supplement)
	010, 012 & 013	May 11, 2001 (Final Draft Labeling)

I. Background

The intention of the August 10, 1999 (S-010) submission is to provide labeling revisions which were written to comply with the provisions of the Geriatric labeling requirements promulgated on August 27, 1999 under 21 CFR 201.57(f)(10).

The intention of the August 30, 2000 submission is to provide for a labeling indication for a shorter treatment course of three days for Valtrex Caplets in the treatment of recurrent episodes of genital herpes.

The intention of the October 27, 2000 (S-013) submission is to revise the label to add coma, decreased consciousness, encephalopathy, psychosis, and visual abnormalities to the Observed During Clinical Practice subsection of ADVERSE REACTIONS. Post-marketing reports (i.e. Medwatch) supporting these changes were submitted with the supplement.

This package insert was compared word to word to the final printed labeling submitted January 21, 2000 (S-009, S-011).

II. Revisions

A. In the **MICROBIOLOGY** section, under **Mechanism of Antiviral Action**, the last sentence in the first paragraph was deleted: "In cell culture, acyclovir's highest antiviral activity is against HSV-1, followed in decreasing order of potency against HSV-2 and VZV."

B. In the **MICROBIOLOGY** section, under **Mechanism of Antiviral Action**, the second paragraph, first sentence was revised to delete EBV. The revised sentence reads: "The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV.

C. In the **MICROBIOLOGY** section, under **Drug Resistance**, the first sentence has been revised. The January 21, 2000 approved label reads: "Resistance of VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase."

The sentence was revised to read: "Resistance of HSV and VZV to acyclovir can result from quantitative and quantitative changes in the viral TK and/or DNA polymerase."

D. In the **MICROBIOLOGY** section, under **Drug Resistance**, the first sentence of the second paragraph currently reads, "antiviral nucleoside analogues". This phrase was replaced with the word, "acyclovir".

E. In the **CLINICAL PHARMACOLOGY** section, under **Metabolism**, the following sentence was deleted. "Neither valacyclovir nor acyclovir metabolism is associated with liver microsomal enzymes." The revised sentence reads, "Neither valacyclovir nor acyclovir is metabolized by cytochrome P450 enzymes.

F. In the **CLINICAL PHARMACOLOGY** section, under **Geriatrics**, the January 21, 2000 approved label reads:

Geriatrics: After single-dose administration of 1 gram of VALTREX in healthy geriatric volunteers, (n = 9, mean age ± SD = 74.0 ± 5.4 years), the half-life of acyclovir was 3.11 ± 0.51 hours, compared to 2.91 ± 0.63 hours in healthy volunteers (n = 33, mean age ± SD = 41.2 ± 10.1 years). Dosage modification may be necessary in geriatric patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

The revised label reads:

Geriatrics: After single-dose administration of 1 gram of VALTREX in healthy geriatric volunteers, the half-life of acyclovir was 3.11 ± 0.51 hours, compared to 2.91 ± 0.63 hours in healthy volunteers. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of VALTREX in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

G. In the **Clinical Trials** section, under **Recurrent Episodes**, the January 21, 2000 approved label reads:

Two double-blind placebo-controlled trials in immunocompetent adults with recurrent genital herpes were conducted. Patients self-initiated therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

In 1 study, patients were randomized to receive 5 days of treatment with either VALTREX 500 mg b.i.d. (n = 360) or placebo (n = 259). The median time to lesion healing was 4 days in the group receiving VALTREX 500 mg versus 6 days in the placebo group, and the median time to cessation of viral shedding in patients with at least 1 positive culture (42% of the overall study population) was 2 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. The median time to cessation of pain was 3 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. Results supporting efficacy were replicated in a second trial.

The revised label reads:

Recurrent Episodes: Three double-blind trials (2 of them placebo-controlled) in immunocompetent adults with recurrent genital herpes were conducted. Patients self-initiated therapy within 24 hours of the first sign or symptom of a recurrent genital herpes episode.

In 1 study, patients were randomized to receive 5 days of treatment with either VALTREX 500 mg b.i.d. (n = 360) or placebo (n = 259). The median time to lesion healing was 4 days in the group receiving VALTREX 500 mg versus 6 days in the placebo group, and the median time to cessation of viral shedding in patients with at least 1 positive culture (42% of the overall study population) was 2 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. The median time to cessation of pain was 3 days in the group receiving VALTREX 500 mg versus 4 days in the placebo group. Results supporting efficacy were replicated in a second trial.

In a third study, patients were randomized to receive VALTREX 500 mg b.i.d. for 5 days (n = 398) or VALTREX 500 mg b.i.d. for 3 days (and matching placebo b.i.d. for 2 additional days) (n = 402). The median time to lesion healing was about 4½ days in both treatment groups. The median time to cessation of pain was about 3 days in both treatment groups.

H. In the **PRECAUTIONS** section, under **Carcinogenesis, Mutagenesis, Impairment of Fertility**, the fourth and the fifth paragraph were revised. The January 21, 2000 approved label reads:

Paragraph 4:
In the mouse lymphoma assay, valacyclovir was negative in the absence of metabolic activation. In the presence of metabolic activation (76% to 88% conversion to acyclovir), valacyclovir was weakly mutagenic.

Paragraph 5:
A mouse micronucleus assay was negative at 250 mg/kg but weakly positive at 500 mg/kg (acyclovir concentrations 26 to 51 times human plasma levels).

The revised label reads:

Paragraph #4:

In the mouse lymphoma assay, valacyclovir was not mutagenic in the absence of metabolic activation. In the presence of metabolic activation (76% to 88% conversion to acyclovir), valacyclovir was mutagenic.

Paragraph #5:
Valacyclovir was not mutagenic in a mouse micronucleus assay at 250 mg/kg but positive at 500 mg/kg (acyclovir concentrations 26 to 51 times human plasma levels).

I. In the **PRECAUTIONS** section, under **Pregnancy: Teratogenic Effects**, in the second paragraph, the number of pregnancies was clarified. In the January 21, 2000 approved label, the sentence reads as follows: "There were 756 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy. The revised label reads, "There were 749 pregnancies followed in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes."

J. In the **PRECAUTIONS** section, under **Pediatric Use**, the January 21, 2000 label reads, "Safety and effectiveness of VALTREX in pediatric patients have not been established. The revised label reads, "Safety and effectiveness of VALTREX in pre-pubertal pediatric patients have not been established.

K. In the **PRECAUTIONS** section, under **Geriatric Use**, the approved January 2000 label reads:

Geriatric Use: Of the total number of patients included in clinical studies of VALTREX, 861 were age 65 or older, and 344 were age 75 or older. A total of 34 volunteers age 65 or older completed a pharmacokinetic trial of VALTREX. The pharmacokinetics of acyclovir following single- and multiple-dose oral administration of VALTREX in geriatric volunteers varied with renal function. Dosage reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

The revised label reads:

Geriatric Use: Of the total number of subjects in clinical studies of VALTREX, 852 were 65 and over, and 346 were 75 and over. In a clinical study of herpes zoster, the duration of pain after healing (post-herpetic neuralgia) was longer in patients 65 and older compared with younger adults. Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have renal or CNS adverse events. With respect to CNS adverse events observed during clinical practice, agitation, hallucinations, confusion, delirium, and encephalopathy were reported more frequently in elderly patients (see CLINICAL PHARMACOLOGY, ADVERSE REACTIONS: Observed During Clinical Practice, and DOSAGE AND ADMINISTRATION).

L. In the **ADVERSE REACTIONS** section, the Tables has been revised. These changes include the following. Table 2 in the January 21, 2000 label is entitled, "Incidence (%) of Adverse Events in Herpes Zoster and Genital Herpes Study Populations." In the revised label, the information contained in Table 2 is now contained in two tables, Table 2 and Table 3. The revised Table 2 is now entitled: "Incidence (%) of Adverse Events in Herpes Zoster Study Populations" and Table 3 is now entitled, "Incidence (%) of Adverse Events in Genital Herpes Study Populations".

Table 3 entitled, "Incidence (%) of Laboratory Abnormalities in Herpes Zoster and Genital Herpes Study Populations", is now Table 4 in the revised label.

M. In the **ADVERSE REACTIONS** section, under **Observed During Clinical Practice**, the following CNS symptoms were added to the revised label: aggressive behavior, coma, decreased consciousness, encephalopathy, and psychosis. In addition, after the word, "psychosis", the label now states, "See **PRECAUTIONS**".

N. In the **ADVERSE REACTIONS** section in the revised label, under **Observed During Clinical Practice**, a category entitled "eye" was added to include visual abnormalities.

O. In the **ADVERSE REACTIONS** section, under **Observed During Clinical Practice**, the term "Hemic" was replaced with the word, "Hematologic".

P. In the section, **DOSAGE AND ADMINISTRATION**, under **Recurrent Episodes**, the first sentence was changed from "500 mg twice daily for 5 days", to "500 mg twice daily for 3 days".

Q. In the section, **DOSAGE AND ADMINISTRATION**, under **Recurrent Episodes**, Table 4 in the January 21, 2000 label is now Table 5 in the revised label.

III. Summary of Review

The revisions to the above referenced VALTREX Caplets are acceptable. In addition, as discussed with Dr. Austin on June 19, 2001, an additional change will be made to the Final Printed Labeling.

In the **VIROLOGY** section, under **Drug Resistance**, the Final Draft Label reads:

[redacted]

The Final Printed Label will read:

"Resistance of HSV and VZV to acyclovir occurs by the same mechanisms."

Please refer to the Medical Officer's memoranda for concurrence. An approval letter will be issued to the Sponsor.

Karen A. Young, RN, BSN
Regulatory Project Manager
Division of Antiviral Drug Products

Attachment: Medical Officer's memoranda
May 10, 2001 Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF FACSIMILE CORRESPONDENCE

Date: **January 16, 2001**

Sponsor: **Glaxo Smith Kline**
Five Moore Drive
Research Triangle Park, NC 27709

Drug: **Valacyclovir hydrochloride (Valtrex®)**

To: **Beth Austin, Ph.D.**
Project Director, Regulatory Affairs

From: **Karen Young, RN, BSN, Regulatory Health Project Manager, DAVDP**

Through: **Sumati Nambiar, M.D., Medical Officer, DAVDP SM ESO 1/12/01**
Rafia Bhore, Ph.D., Mathematical Statistician
Therese Cvetkovich, M.D., Medical Team Leader, DAVDP

Subject: **Request for information NDA 20-550, Supplement Number: S-012**

The following request pertains to your supplemental NDA 20-550 (S-012) dated August 30, 2000.

We are requesting the following information for the label:

1. In Table 3, please provide the number of patients (n) in each individual study of genital herpes for both dosing groups of Valtrex and placebo.

2. Please provide a listing of adverse events in 34-526-028 (NDA 20-550) by number of patients and by the three treatment groups.

3. Please clarify if preferred terms such as diarrhea, loose stool and frequent defecation are combined into one single preferred term, i.e. diarrhea. Please provide the combined incidence of these adverse events.

4. In the section describing the pregnancy registry, please verify that the correct number of pregnancies is represented.

January 16, 2001

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.

Karen A. Young, RN, BSN
Regulatory Project Manager
Division of Antiviral Drug Products

Karen Young
1/16/01 02:10:36 PM
CSO

This is the fax that we sent today re: Valtrex label.

Therese Cvetkovich
1/16/01 02:12:30 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **December 1, 2000**

To: **Beth Austin, Ph.D.**
Project Director, Regulatory Affairs

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

From: **Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP**

Through: **Therese Cvetkovich, MD, Medical Team Leader**
Sumati Nambiar, MD, Medical Officer, DAVDP

Subject: **Request for information NDA 20-550, Supplement Number: S-012**

The following request pertains to your supplemental NDA 20-550, number S-012 dated August 30, 2000.

Table 4 entitled "Number of Major Deviations/Violations of the Protocol for All Randomized Patients" (volume 2, page 97), contains six categories of protocol deviation or violation, one of which is entitled "other". Please provide a detailed listing of the reasons subjects were included in the category "other" in this table.

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.

Karen A.Young, RN, BSN
Regulatory Project Manager
Division of Antiviral Drug Products

Karen Young
12/1/00 11:53:59 AM
CSO

fax requesting additional info

Therese Cvetkovich
12/1/00 01:05:49 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **November 14, 2000**

To: **Beth Austin, Ph.D.**
Project Director, Regulatory Affairs

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

From: **Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP**

Through: **Therese Cvetkovich, MD, Medical Team Leader ESO TC 11/9/00**
Sumati Nambiar, MD, Medical Officer, DAVDP

Subject: **Request for information NDA 20-550, Supplement Number: S-012**

The following request pertain to your supplemental NDA 20-550, supplement number S-012 dated August 30, 2000.

We are requesting the following information:

1. Please identify which study investigators who participated in the study HS2A4004 have also participated in other valacyclovir studies.

2. Please identify which sites the Division of Scientific Investigations has inspected during previous NDA reviews of valacyclovir.

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.

Karen A.Young, RN, BSN
Regulatory Project Manager
Division of Antiviral Drug Products

Karen Young
11/16/00 03:55:47 PM
CSO

Fax to Glaxo Wellcome requesting additional info.

Therese Cvetkovich
11/20/00 12:20:07 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **October 17, 2000**

To: **Beth Austin, Ph.D.**
Project Director, Regulatory Affairs

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

From: **Karen A. Young, RN, BSN, Regulatory Project Manager, DAVDP**

Through: **Therese Cvetkovich, MD, Medical Team Leader**
Sumati Nambiar, MD, Medical Officer, DAVDP
Greg Soon, Ph.D, Mathematical Statistician Team Leader, DAVDP
Rafia Bhore, Ph.D., Mathematical Statistician, DAVDP

Subject: **Comments for NDA 20-550, Supplement Number: S-012**

The following comments/requests pertain to your supplemental NDA 20-550, supplement number S-012 dated August 30, 2000.

We are requesting the following information be sent to the Agency by October 30, 2000:

1. Please submit the demographics dataset(s).

2. Please submit the efficacy dataset(s), including the following:

   - Raw data containing efficacy measurements,
   - Raw data containing laboratory measurements (if any),
   - Programs transforming raw data into intermediate analysis datasets, and
   - Programs, algorithms, and macros (if any) using intermediate analysis datasets to obtain efficacy results.

4. Please submit the safety dataset(s), including raw data containing safety variables as well as the programs for obtaining results on safety parameters.

5. Please submit clear and concise documentation of variables. Also include comments in programs in order to make them readable and understandable.

6. Please submit the SAS Transport files on CD-ROM. One dataset per SAS Transport file

is preferred. SAS files will need to be compatible with Microsoft Windows 95 SAS version 6.12.

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.

Karen A.Young, RN, BSN
Regulatory Project Manager
Division of Antiviral Drug Products

cc:
Original NDA 20-550

Division File NDA 20-550
HFD-530/MO/Nambiar
HFD-530/Stats/Bhore
HFD-530/RPM/Young

NDA 20-550

DAVDP/HFD-530 . 5600 Fishers Lane . Rockville, MD 20857 . (301) 827-2335 . Fax: (301) 827-2523

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Memorandum of 45 day Filing Meeting

Date: October 17, 2000

Drug: Valtrex Caplets® (Valacyclovir hydrochloride)

Indication: Treatment of recurrent genital herpes

Dosage: Valtrex Caplets® 500 mg BID x 3 days

NDA: 20-550 (S-012)

Sponsor: Glaxo Wellcome

FDA Participants:

Heidi Jolson, M.D., M.P.H., Division Director
Debra Birnkrant, M.D., Deputy Director
Walla Dempsey, Ph.D., Deputy Director
Anthony DeCicco, R.Ph., Supervisory Project Manager
Therese Cvetkovich, M.D., Medical Team Leader
Sumati Nambiar, M.D., Medical Officer
James Farrelly, Ph.D., Pharmacology Team Leader
Ko-Yu Lo, Ph.D., Chemistry Reviewer
Greg Soon, Ph.D., Statistical Team Leader
Rafia Bhore, Ph.D., Statistical Reviewer
Kellie Reynolds, Pharm.D., Biopharmaceutical Team Leader
Jooran Kim, Pharm.D., Pharmacokinetics Reviewer
Rebecca Sheets, Ph.D., Microbiology Team Leader
Melissa M. Truffa, R.Ph., Regulatory Project Manager
Karen A. Young, RN, BSN, Project Manager

Background

The purpose of this meeting is to discuss the filing of efficacy supplement S-012, which provides for a 3-day course of Valtrex® for the treatment of recurrent genital herpes. As previously agreed with the Division, this supplemental NDA is supported by clinical data from study HS2A4004.

Discussions

1. **Pharmacology/Toxicology**: Filable. No new pharmacology/toxicology data submitted with this sNDA.

2. **Microbiology**: Filable. No new microbiology data submitted with this sNDA.

3. **Clinical Pharmacology/Biopharmaceutics**: Filable. No new clinical pharmacology/biopharmaceutics data submitted with this sNDA.

4. **Chemistry**: Filable. No new CMC data submitted with this sNDA.

5. **Statistical**: Filable. Division will request electronic SAS datasets.

6. **Clinical**: Filable. Division will request a random sampling of CRFs.

7. **DSI Audit**: No plans for DSI audit at this time.

Conclusion

The review team concluded that the efficacy supplement (S-012) for NDA 20-550 is filable. The sponsor will be notified of our decision to file this efficacy supplement.

Action Items

1. Statistical comment requesting electronic SAS datasets will be sent to the sponsor with request date no later than October 30, 2000.

2. Will request a random sampling of CRFs.

3. Will obtain review of the original protocol for study HS2A4004.

Signature, minutes preparer: _____

Date: _____

Karen Young
10/23/00 04:24:17 PM
CSO

Fax sent to GW requesting additional statistical data. NDA 20-550/SE2 /012, shorter Valtrex tx course for recurrent genital herpes.

Greg Soon
11/7/00 05:10:09 PM
BIOMETRICS