CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20550/S-003

Trade Name: VALTREX

Generic Name: VALACYCLOVIR HYDROCHLORIDE

Sponsor: GLAXO WELLCOME

Approval Date: SEPTEMBER 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20550/S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20550/S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-550/S-003

Glaxo Wellcome Inc.
Attention: Robert S. Watson
5 Moore Drive
Research Triangle Park, NC 27709

SEP 26 1997

Dear Mr. Watson:

Please refer to your November 18, 1996 supplemental New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VALTREX™, (valacyclovir hydrochloride) 500 mg and 1 gm Caplets.

We acknowledge receipt of your submissions dated:

February 13, 1997	July 25, 1997	September 17, 1997
February 24, 1997	August 8, 1997	
April 11, 1997	August 13, 1997	

The User Fee goal date for this application is November 19, 1997.

This supplemental drug application provides for the suppression of recurrent episodes of genital herpes in immunocompetent adults.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the September 25, 1997 draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on September 25, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-550/S-003. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact Melissa M. Truffa, R.Ph., Regulatory Health Manager at (301) 827-2335.

Sincerely yours,

Debra Birnkrant, M.D.
Acting Director
Division of Antiviral Drug Product
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20550/S-003

MEDICAL REVIEW(S)

DRAFT

MEDICAL OFFICER REVIEW

NDA 20-550 S-003

(DRAFT September 25, 1997)

DRAFT

Date submitted: November 18, 1996
Date received: November 20, 1996
Date assigned: November 21, 1996
MOR completed:
Revisions completed:

Sponsor: Glaxo Wellcome Co.
3030 Cornwallis Road
P.O. Box 12700
Research Triangle Park, N.C. 27709

Drug:

Generic: Valacyclovir hydrochloride
Trade: Valtrex ™
Chemical: (2-[(2-amino-1,6-dihydro-6-oxo-9-purin-yl)methoxy]ethyl-l-valinate hydrochloride
Other names: valaciclovir
256U87 hydrochloride

Dosage form: caplet
Strength: 500 mg
Route: oral

Proposed indication: Suppression of recurrent genital herpes

Related IND:

Related NDA's: 20-487
20-550
20-550-S001

RESUME

The results of two double-blind, randomized, acyclovir-controlled trials in — immunocompetent patients with recurrent genital herpes were submitted by the applicant in support of the claim that valacyclovir is safe and effective for the suppression of recurrent genital herpes. Efficacy was assessed by evaluation of the proportion of patients recurrence-free at one year of treatment.

Valacyclovir's efficacy for the treatment of recurrent genital herpes was supported by the demonstration of efficacy for all doses of valacyclovir studied. Similar efficacy was observed for the 1000 mg QD valacyclovir doses when compared to acyclovir 400 mg BID in the proportion of subjects free of recurrences at one year in study 026. Valacyclovir had an acceptable safety profile in this young and healthy population. Based on these findings, and because the has not been approved for marketing, this application for valacyclovir 1000 mg po QD for the chronic suppression of recurrent genital herpes should be approved. An alternative dose of 500 mg daily is supported for patients who have experienced nine or fewer recurrences per year.

BACKGROUND

Regulatory history

The IND for valacyclovir hydrochloride was submitted in March 1990. Valacyclovir 1000 mg po TID for seven days (NDA 20-487) was approved for the treatment of herpes zoster in immunocompetent adults June 24, 1995. Valacyclovir 500 mg po BID for five days (NDA 20-550) was approved December, 1995 for the treatment of recurrent episodes of genital herpes. Valacyclovir 1000 mg po BID for 10 days (NDA 20-550-S001) for the treatment of first episode genital herpes was approved October 9, 1996.

Recurrent genital herpes: natural history and treatment

Genital herpes infections recur frequently after primary infection with either HSV-1 or HSV-2. These recurrences are caused by activation of latent virus in the sacral ganglia and are more common following primary infection with HSV-2. The risk of recurrence after the initial episode of genital herpes due to HSV-2 is 80%, and is 50% after initial episodes due to HSV-1. Systemic symptoms and local involvement tend to be milder with recurrent episodes. A prodrome of tenderness, itching, burning or tingling may precede the development of lesions by several hours. Healing is quicker with recurrences and generally occurs within 6-10 days. Recurrences are typically more severe in women.

Oral acyclovir therapy for the first episode of genital herpes reduces the duration of viral shedding, pain, time to healing, and the incidence of new lesion formation, but does not prevent recurrence in the absence of continued suppressive therapy. Acyclovir has only a modest effect on recurrent episodes; reducing the duration of episodes by one day when therapy is initiated early. Therapy is not recommended for most episodes of recurrent herpes in immunologically competent hosts. In patients with very frequent or severe recurrent

episodes, or those whose recurrent episodes are associated with severe complications (erythema multiforme, recurrent aseptic meningitis, eczema herpeticum) suppressive therapy is of benefit. Oral acyclovir is approved for the suppression of genital herpes; the dose is 400 mg BID, with re-evaluation every six months to a year.

CLINICAL IMPLICATIONS OF PRE-CLINICAL STUDIES

Chemistry/ Manufacturing Control

(This section was cross-referenced to NDA 20-487; no new studies were submitted.)

Animal Pharmacology/ Toxicology

(This section was cross-referenced to NDA 20-487; no new studies were submitted.)

Microbiology

(This section was cross-referenced to NDA 20-487; no new studies were submitted.)

CLINICAL IMPLICATIONS OF HUMAN BIOPHARMACOLOGY STUDIES

Two drug interaction studies, evaluating the potential for interactions between valacyclovir and digoxin or antacids, were submitted with this SNDA. No interactions in acyclovir pharmacokinetics were observed following single-dose administration of valacyclovir 1000 mg with antacids or digoxin. No dose adjustment of valacyclovir is required with co-administration of either of these agents. Please refer to Dr. Davit's review for a more detailed review of these data.

OVERVIEW OF CLINICAL DATA SECTION

The results of two studies were submitted in support of this application; study 123-026, which will be presented below, and study 123-037. Study 037 compared valacyclovir 500 mg once daily with placebo for four months in patients with greater than eight HSV recurrences per year. Because the duration of four months was too brief to contribute additional efficacy data to that provided by Study 026, efficacy data from Study 037 will not be further discussed.

The integrated summary of safety submitted in this application included data from three studies of suppression of recurrent genital herpes in otherwise healthy adults, two ongoing studies of treatment or suppression of genital herpes in HIV-infected adults, three ongoing studies of suppression of CMV disease in bone marrow- or renal-transplant patients, and four post-marketing herpes zoster studies in immunocompetant adults. Post-marketing surveillance reports are also included. The safety database cut-off date for this application was June 1, 1996.

STUDY 123-026

Objectives

The protocol objectives were to evaluate the efficacy and safety of four doses of valacyclovir compared to acyclovir and placebo for the suppression of recurrent genital herpes in otherwise healthy adults.

Design

This was a randomized, double-blind, multicenter, international trial in which healthy adults with recurrent genital herpes (≥ six episodes in the previous year) were randomized to one of six treatment arms and followed for one year. Valacyclovir doses were : BID, 1000 mg QD, 500 mg QD and QD, and the acyclovir dose was 400 mg BID. Randomization allocation was 2:2:2:2:2:1 with twice as many subjects assigned to each treatment arm as to the placebo arm.

Comment: It should be noted that the dosage form is not currently marketed.

Endpoints

The protocol-designated primary efficacy endpoint was the time to first recurrence of a genital herpes episode. The endpoint recommended by FDA, proportion of patients recurrence-free at 12 months, was also evaluated. The secondary endpoint was time to second recurrence.

Comment: For the purposes of this review, the evaluation of the time to first recurrence endpoint will be considered to be a secondary endpoint. FDA recommended evaluation of the proportion of patients recurrence-free at 12 months as the more preferable endpoint because of its clinical relevence and more straightforward statistical analysis.

Procedures

Subjects were evaluated at monthly study visits and on days 1 and 5 of a genital herpes recurrence (if possible). Subjects were asked to record the date of the onset of lesions if unable to report to the clinic with a recurrence. At each monthly visit subjects were queried about episodes of genital herpes for which they did not report to the clinic and the date of onset of lesions for that recurrence was recorded in the CRF.

A viral culture of lesions was obtained on day 1 of any genital herpes recurrence. HSV was identified in culture by cytopathic effect; virus typing was not required.

Plasma acyclovir samples were obtained at months 3, 6, 9, and 12, or at study discontinuation.

Safety assessment

Blood for chemistry (creatinine, alkaline phosphatase, and ALT) and hematology (hemoglobin, white blood cell count and platelets) was obtained at screen, and months 6 and 12, or at study discontinuation. Serum creatinine was also evaluated at month 3. Female patients of child-bearing potential were tested for pregnancy at screen, and at months 3, 6, 9 and 12, or at study discontinuation.

Adverse experiences were documented at the monthly clinic visit.

Statistical consideration

SAMPLE SIZE

Sample size calculation was based on the primary endpoint of time to first recurrence. The sample size of 100 placebo patients provided at least 80% power to detect a difference between 0.45 and 0.05 in the proportion of patients recurrence-free at one year in a comparison of an active treatment arm and the placebo arm.

ANALYSIS

The principal efficacy analyses included the intent-to-treat population, defined as all randomized patients. For analysis of the proportions of patients recurrence-free at 12 months, all unknowns were assumed to have had a recurrence. The Cochran-Mantel-Haentszel test, stratified by site, was conducted to test for specified treatment differences in the proportions of patients recurrence-free at 12 months.

In addition, results were analyzed by the Kaplan-Meier product-limit method, and differences between groups were assessed by Cox's proportional hazards model adjusted for center and HSV-recurrence history.

A subset analysis also excluded patients with protocol violations (efficacy subset group).

RESULTS

Patient disposition, comparability

The study was conducted between April 1994 and January 1996. A total of 1479 patients at 53 sites was enrolled and randomized to treatment: 269 to valacyclovir BID, 269 to valacyclovir 1000 mg QD, 266 to valacyclovir 500 mg QD, 269 to valacyclovir QD, 267 to acyclovir 400 mg BID, and 134 to placebo. One thousand and fifty subjects completed the study.

Overall, patient demographics were balanced between treatment groups. The median age at screening was 34 years (range: 17 to 85). Fifty-two percent of the subjects were female with a slightly higher proportion of female subjects in the placebo group (59%). Eighty-seven percent of subjects were white, 8% black, and 5 % were other races. Pre-treatment medical history, screening physical exam, and baseline clinical laboratory results were similar between the treatment groups.

A summary of genital herpes infection history is provided in Table 1. In general, subject histories were comparable, with the exception of a somewhat decreased proportion of subjects with greater than nine episodes per year enrolled in the valacyclovir 500 QD group.

TABLE 1. STUDY 026: GENITAL HERPES INFECTION HISTORY

	Vacv BID N=274	Vacv 1000 QD N=269	Vacv 500 QD N=266	Vacv QD N=269	Acv 400 BID N=266	Placebo N=134
Years from 1st episode (mean)	7.3	7.6	6.9	6.8	6.8	7.8
HSV documentation (%) Pos culture	36	39	41	39	42	39
Written confirm.	58	54	52	48	52	54
Other confirm.	21	20	19	23	21	17
# Recurrences prev. year (%)						
1-5	3	2	4	2	4	3
6-9	56	53	65	59	52	56
>9	41	45	32	39	44	41
Suppressive tx prev. year (%)	15	15	15	13	17	16

Accountability of all patients enrolled in Study 026 is shown in Table 2.

TABLE 2. STUDY 004: PATIENT ACCOUNTABILITY

	Vacv BID	Vacv 1000 QD	Vacv 500 QD	Vacv QD	Acv 400 QD	Placebo
Randomized (N)	274	269	266	269	267	134
Normal completion (N)	202 (74%)	201 (75%)	194 (73%)	183 (68%)	197 (74%)	73 (54%)
Premature discontinuation (N)	72 (26%)	68 (25%)	72 (27%)	86 (32%)	70 (26%)	61 (46%)
Premature discontinuations (N)	72	68	72	86	70	61
Reasons: (N)						
Adverse experience	11	15	14	16	12	8
Death	0	0	0	0	0	0
Inadequate response	6	5	2	16	4	23
Consent withdrawn	19	22	25	24	25	11
Lost to follow up	30	19	25	23	24	15
Protocol violation	6	7	6	7	5	4

Frequencies and reasons for premature discontinuations in general were distributed evenly among the treatment groups. A higher proportion of subjects in the placebo arm discontinued prematurely; the most frequent reason was inadequate response to therapy. Also, proportionally fewer patients in the placebo group were lost to follow up.

Results of primary efficacy analysis

Only the intent-to-treat analyses will be presented and evaluated because analysis of the intent-to-treat and efficacy subsets were generally similar. Center effects will not be discussed, as important differences between center-stratified analyses were not detected.

The proportion of patients recurrence-free at 6 and 12 months is provided in Table 3.

TABLE 3: STUDY 028: PROPORTION OF PATIENTS RECURRENCE-FREE AT SIX AND TWELVE MONTHS.

Treatment Group	Six months		Twelve months	
	N. Recurrence free (%)	N. Unknown (%)	N Recurrence free (%)	N Unknown (%)
Vacv BID (274)	147 (54)	36 (13)	94 (34)	60
Vacv 1000 QD (269)	148 (55)	27 (10)	92 (34)	52
Vacv 500 QD (266)	123 (46)	27 (10)	75 (28)	47
Vacv QD (269)	70 (26)	35 (13)	40 (15)	45
Acv 400 BID (267)	144 (54)	27 (10)	92 (35)	51
Placebo(134)	134 (7)	14 (10)	6 (5)	14

The relative risks, 95% confidence intervals, and p-values for the primary endpoint of proportion of patients recurrence-free at 12 months compared to placebo is given in Table 4.

TABLE 4. STUDY 028: RELATIVE RISKS FOR PATIENTS RECURRENCE-FREE AT SIX AND TWELVE MONTHS.

Dose	Relative Risk	95% C.I.	p-value
Vacv BID	0.629	[0.551, 0.719]	<0.001
Vacv 1000 QD	0.650	[0.572, 0.739]	<0.001
Vacv 500 QD	0.690	[0.604, 0.787]	<0.001

Dose	Relative Risk	95% C.I.	p-value
Vacv QD	0.841	[0.752, 0.942]	0.003
Acv 400 BID	0.641	[0.561, 0.732]	not tested

Kaplan-Meier estimates of the proportion of patients who were recurrence-free at 12 months were consistant with the results of the proportional analysis described above. Since the Kaplan-Meier estimates of the proportion of patients recurrence-free at 12 months for the valacyclovir BID, 1000 mg QD, and acyclovir 400 mg BID groups were converging on 50%, reliable estimates of the median time to first recurrence could not be made. For the valacyclovir 500 mg QD, mg QD and placebo groups, the medians were 203, 96, and 31 days, respectively.

Results of subgroup/exploratory analyses

Gender, age (<34 years, ≥ 34 years), and previous recurrence history (≤ 9 episodes/year, > 9 episodes/year) were investigated as factors with potential prognostic significance. The small number of patients designated black/other did not allow for analysis of race as a possible co-factor.

Gender was found to be a significant modifier of the treatement effect; men had higher recurrence-free rates than women for all the treatment groups. Significant effects were not demonstrated for the analysis of age. Relative treatment differences in the HSV history sub-groups were demonstrated for the ng BID vs. 1000 mg QD or 500 mg QD comparisons, but not for the 1000 mg QD vs 500 mg QD comparison.

The valacyclovir treatments were compared to acyclovir in analyses performed by the FDA statistical reviewer. The BID dose was more efficacious in those with nine of fewer recurrences per year, whereas acyclovir 400 mg BID was more efficacious in those with 10 or more episodes per year. Valacyclovir 500 mg QD was less efficacious than acyclovir 400 mg BID in patients with 10 or more episodes per year.

EVALUATION OF SAFETY

Deaths

One patient in the valacyclovir . QD group died of bronchial asthma during the study.

Treatment limiting adverse events

Sixty-two subjects (6%) assigned to the valacyclovir arms, 14 subjects (5%) assigned to the acyclovir arm, and eight subjects (6%) assigned to the placebo group experienced an adverse

event that led to discontinuation of treatment. The distribution and nature of these events were similar among the treatment groups.

Serious adverse events

Thirty-six subjects (3%) assigned to the valacyclovir treatment arms experienced 45 serious adverse events, 4% in the BID group, 3% in the 1000 QD group, 4 % in the 500 QD group, and 3% in the QD group. Ten subjects (4%) assigned to the acyclovir arm experienced 12 serious adverse events, and two subjects (1%) assigned to the placebo group experienced three serious adverse events. The types of serious adverse events were similar among the treatment groups.

Adverse events

Among subjects assigned to the valacyclovir groups, 84% of those in the valacyclovir BID group, 84% of those in the valacyclovir 1000 QD group, 88% of those in the valacylovir 500 mg group, and 82% of those in the valacyclovir QD group reported adverse events. Eighty-five percent of those in the acyclovir group and 81% of those in the placebo group experienced adverse events. Headache, rhinitis, infections, flu syndrome, pharyngitis, nausea, back pain

Pregnancy outcome

Fourteen women became pregnant during the conduct of this trial. Thirteen had first trimester exposure to either valacyclovir or acyclovir; one subject received placebo. Outcomes for these pregnancies are as follows: three were lost to follow up, three had spontaneous abortions, six had induced abortions, and two had normal infants. One of the two had the complication of premature atrial contractions.

Laboratory abnormalities

Inspection of descriptive statistics, quartile plots, and change from baseline quartile plots did not reveal differences among the treatment groups with regard to clinical chemistry (creatinine, alkaline phosphatase, and ALT), or hematology (hemoglobin, white blood cell count, and platelets).

Pharmacokinetics

Table 5 shows the estimated pharmacokinetic parameters for the five dosage regimens. For the once daily regimens, increasing peak concentrations and AUCs of acyclovir were associated with the increasing valacyclovir doses.

TABLE 5: STUDY 026: PHARMACOKINETIC PARAMETERS

Drug regimen	Daily AUC (μg·hr/mL)	Cmax (μg/mL)
Valacyclovir BID	12.39	1.57
Valacyclovir 1000 QD	18.13	5.13
Valacyclovir 500 QD	10.35	2.48

Drug regimen	Daily AUC (µg·hr/mL)	Cmax (µg/mL)
Valacyclovir . QD	4.95	1.36
Acyclovir 400 BID	7.60	0.67

Table 6 shows acyclovir exposures of the study treatments based on two potentially relevant threshold concentrations: 1) an average of in vitro sensitivities of HSV Type 2 in plaque reduction assays (approximately 1.13 µM); and 2) the trough acyclovir concentration from the acyclovir BID regimen.

TABLE 6: ACYCLOVIR EXPOSURE

Drug regimen	Time (hours) above average in vitro IC 50	Time (hours) above acyclovir 400 mg BID trough
Valacyclovir . 3ID	13.4	24
Valacyclovir 1000 QD	10.5	17.1
Valacyclovir 500 QD	8.8	15.3
Valacyclovi QD	6.6	13.1
Acyclovir 400 BID	10.7	24

CONCLUSIONS FROM STUDY 026

The proportions of patients recurrence-free at 12 months were identical for the valacyclovir mg BID, 1000 mg QD, and the acyclovir 400 mg BID groups: 34%. The proportions recurrence-free at 12 months for the 500 mg QD group and . mg QD groups were 28% and 15%. In comparison, the proportion recurrence-free at 12 months was 4% in the placebo group. All valacyclovir doses were effective when compared to placebo. The mg BID and 1000 mg QD dosing regimens were as effective as the approved treatment, acyclovir 400 mg BID. The 500 mg QD dose was effective, though somewhat less than the acyclovir regimen. The . mg QD dose was less effective than the acyclovir 400 mg BID regimen.

Efficacy results were concistant with the pharmacokinetic data. These data would suggest that the duration that acyclovir concentrations exceed a threshold concentration (though the appropriate parameter is not known) constitutes an important pharmacokinetic correlate of efficacy. That is, though the QD dosing regimens showed increasing efficacy with increasing dose, those regimens that maintained plasma acyclovir concentrations for the greatest duration were the most efficacious.

The sponsor has requested approval of the 500 mg QD day dose, with 1000 mg QD dosing recommended for those with 10 or more episodes per year. However, sub-group analysis of recurrence history in the analysis of proportion recurrence-free was not supported statistically, so that comparison of these two doses should be based on the overall recurrence-free rates. In that analysis, as noted above, the 1000 mg QD dose was more efficacious than the 500 mg QD dose. Because it is likely that patients choosing to initiate chronic suppressive treatment will have experienced multiple frequent and/or severe recurrences, approval of 1000 mg QD will provide the most efficacious of the regimens that may be prescribed. For those whose recurrences are somewhat less frequent or troublesome, but who choose chronic suppression, it is likely given the data provided, that the 500 mg QD dose will provide adequate suppression at a lower total daily dose.

Adverse experiences were generally mild and did not require discontinuation of study medication. Laboratory evaluation did not reveal clinically important changes in laboratory parameters over the study period. Results of the safety analyses were consistent with the current product label.

SAFETY OVERVIEW

Safety data provided in safety update for this NDA does not change the assessment of safety provided in the clinical review of study 026.

LABELING COMMENTS

Because of numerous reports from post-marketing surveillance of renal failure and CNS symptoms occurring in cases of inadvertant overdosage, wording of the appropriate sections of the label have been strenghthened.

RECOMMENDED PHASE IV COMMITMENTS

RECOMMENDATION FOR APPROVAL

Based on information submitted in NDA 20-550 S003, this application for valacyclovir 1000 mg po QD for the suppression of recurrent genital herpes in healthy adults should be approved.

Therese Cvetkovich, M.D.
Medical Officer, Division of Antiviral Drug Products

Concurrences:
HFD-530/Acting Div Dir/DFreeman
HFD-530/TL/RBehrman

CC:
HFD-530/NDA 20-550
HFD-530/DivFile
HFD-530/Biopharm/BDavits
HFD-530/PharmTox/
HFD-530/Micro/NBiswal
HFD-530/Chem/KLo
HFD-530/Stat/LKammerman
HFD-530/Stat/THammerstrom
HFD-530/CSO/DStaten
HFD-530/MO/TCvetkovich
HFD-340

July 20, 1997
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20550/S-003

CHEMISTRY REVIEW(S)

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls Section

NDA #: 20-550 /SEI 003

CHEMISTRY REVIEW #: 1 **DATE REVIEWED** 26-JUN-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SEI003(Original)	18-DEC-96	19-DEC-96	NA

NAME/ADDRESS OF APPLICANT: Glaxo Wellcome Inc..
Five Moore Drive
Research Triangle Park, NC 27709

DRUG PRODUCT NAME

Proprietary:	Valtrex™
Nonproprietary:	Valacyclovir hydrochloride
Code Name/#:	256U87 hydrochloride
Chem. Type/Ther. Class:	2S

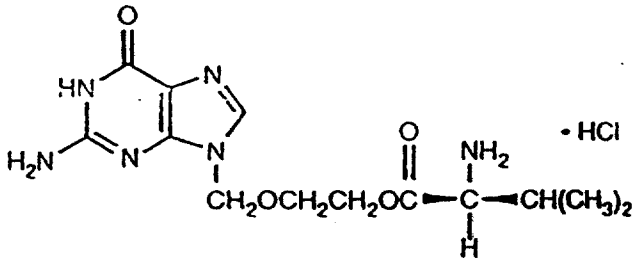
PHARMACOLOGICAL CATEGORY: Antiviral

INDICATION: Suppressive Therapy for Genital Herpes Simplex Virus Infections

DOSAGE FORM/STRENGTH: Caplets/500 mg & 1000 mg

ROUTE OF ADMINISTRATION: PO

CHEMICAL NAME/STRUCTURAL FORMULA:
L-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester, monohydrochloride



Molecular Weight:	360.80	324.34 (free base)
Empirical Formula:	$C_{13}H_{20}N_6O_4$ HCl	$C_{13}H_{20}N_6O$

RELATED DOCUMENTS: NDA 20-487 Chemist's Review #1,2, & 3
NDA 20-550 Chemist's Review #1

SUMMARY/CONCLUSIONS/RECOMMENDATIONS:

Chemistry, manufacturing and controls (CMC) information regarding the new drug substance and the Valtrex Capsules have been reviewed and found acceptable in the approved NDAs 20-487 and 20-550. Analytical results for the drug substance and drug product batches used in clinical trials for HSV suppression was found acceptable.

The supplemental environmental assessment (EA) report was found acceptable. A FONSI (Finding of No Significant Impact) has been issued. A FONSI/EA Report/EA Review are attached to this review.

The chemistry section of the proposed labeling is found acceptable.

In conclusion, the chemistry section for SEI001 is approved from a CMC standpoint.

Ko-Yu Lo

Ko-Yu Lo, Ph.D., Review Chemist

Concurrence:
HFD-530/SMiller SMiller 8/25/97
cc:
Orig. NDA 20-550
HFD-530/Div. File
HFD-530/KYLo
HFD-530/SMiller
HFD-530/MO
HFD-530/Pharm
HFD-530/Micro
HFD-530/CSO

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20550/S-003

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

VALTREX™

(valacyclovir hydrochloride)

Caplets

NDA 20-550/SE1003

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-550/SE1003

VALTREX™
(valacyclovir hydrochloride)
Caplets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for VALTREX Caplets, Glaxo Wellcome, Inc. has prepared an environmental assessment in accordance with 21 CFR 25.31a (a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

VALTREX (valacyclovir hydrochloride) Caplets is indicated for suppressive therapy for genital herpes simplex virus infection. The drug product will be used in hospitals and at home throughout the US.

The drug substance will be manufactured by Glaxo Wellcome Inc, at Greenville, NC, USA and Dartford, Kent, UK. The drug product will be manufactured at Greenville, NC, USA.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or rejected drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

6/26/97 Koyu Lo
DATE PREPARED BY:
Ko-Yu Lo
Review Chemist
Division of New Drug Chemistry III

6/26/97 Paul Jin (for Stephen Miller)
DATE DIVISION CONCURRENCE:
Stephen P. Miller, Ph.D.
Team Leader
Division of New Drug Chemistry III

7/10/97 Nancy B. Sager
DATE CONCURRED:
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet (drug substance)

NON-CONFIDENTIAL

ENVIRONMENTAL ASSESSMENT REPORT

VALTREX™ (valacyclovir hydrochloride) Caplets

NDA 20-550/SE1003

TABLE OF CONTENTS

1. DATE

October 30 1996

2. APPLICANT

Glaxo Wellcome Inc.

3. ADDRESS

Five Moore Drive
Research Triangle Park, NC 27709

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Description of Requested Approval

Glaxo Wellcome Inc. has filed a supplement to NDA 20-550 pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for VALTREX® (valacyclovir hydrochloride). On December 19, 1994, Glaxo Wellcome submitted NDA 20-550 requesting approval to market VALTREX® (valacyclovir hydrochloride) Caplets for the treatment of recurrent genital herpes. This NDA submission included an environmental assessment (EA) pursuant to 21 CFR Part 25.31 a(a). On December 15, 1995 FDA approved NDA 20-550. As provided for in the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), this supplemental EA discusses only the impact of the new indication on the environmental assessment submitted with NDA 20-550.

Glaxo Wellcome Inc. also filed NDA 20-487 VALTREX® Caplets to be marketed for treatment of herpes zoster on June 23, 1994 and received approval on June 23, 1995.

4.b. Need for the Action

Valacyclovir hydrochloride is indicated for the treatment of herpes zoster, and initial and recurrent episodes of genital herpes. The requested approval will allow the product to be marketed for the suppression of herpes simplex virus.

4.c. Locations where Products will be Produced

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4.d of the original EA for VALTREX® (valacyclovir hydrochloride) 500 and 1000 mg Caplets as included in NDA 20-550 approved on December 15, 1995.

4.d. Sites of Product Use

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4.d of the original EA for VALTREX® (valacyclovir hydrochloride) 500 and 1000 mg Caplets as included in NDA 20-550 approved on December 15, 1995.

4.e. Sites of Disposal

Returned and expired drug product is destroyed at the Glaxo Wellcome facility in Greenville, North Carolina. The facility is located northeast of the city of Greenville in Pitt County, North Carolina at the intersection of U.S. 13 North and State Road 1590. Pitt County is located in eastern North Carolina. The city of Greenville, with an estimated 1990 population of 48,000, is located in the center of the county approximately 50 kilometers southeast of Rocky Mount. Since the plant site is located in the coastal plain region of the state, terrain is extremely flat with terrain elevations changing only a few feet within a few kilometers of the plant site. The facility is located in an area zoned industrial. To the West-Northwest of the facility the land is zoned Residential/Agricultural. The returned drug is destroyed by a controlled air incinerator which operates at temperatures ranging from at least 1200°F in the primary chamber to 1850°F in the secondary chamber. The incinerator operates under permit number 74-03-I issued by the N.C. Division of Solid Waste. The permit expires July 7, 1997. The address of the facility is:

Glaxo Wellcome Inc.
Corner of U.S. 13/NC11 and State Road 1590
Greenville, North Carolina 27834

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4.d of the original EA for VALTREX® (valacyclovir hydrochloride) 500 and 1000 mg Caplets as included in NDA 20-550 approved on December 15, 1995.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.a. Substances Expected To Be Emitted

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4.d of the original EA for VALTREX® (valacyclovir hydrochloride) 500 and 1000 mg Caplets as included in NDA 20-550 approved on December 15, 1995.

6.b. Controls Exercised

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4.d of the original EA for VALTREX® (valacyclovir hydrochloride) 500 and 1000 mg Caplets as included in NDA 20-550 approved on December 15, 1995.

6.c. Citation And Statement Of Compliance With Applicable Emission Requirements

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4.d of the original EA for VALTREX® (valacyclovir hydrochloride) 500 and 1000 mg Caplets as included in NDA 20-550 approved on December 15, 1995.

6.d. Effect Of Approval On Compliance With Current Emission Requirements

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4.d of the original EA for VALTREX® (valacyclovir hydrochloride) 500 and 1000 mg Caplets as included in NDA 20-550 approved on December 15, 1995. Although more drug product may be needed to support the requested approval, emission requirements are based on emissions concentrations. Per batch emission concentrations will remain unchanged.

6.e. Expected Introduction Concentrations

6.e.i. Expected Introduction Concentrations From Use

Calculations of the Expected Introduction Concentration (EIC) for the aquatic compartment are included as confidential information in Attachment A. Attachment A shows that the EIC, calculated using the amount of drug substance needed to support the maximum production numbers from the most recent marketing forecast for all valacyclovir dosage forms and all indications including suppression of genital herpes simplex, is less than the EIC projected in the original EA.

6.e.ii. Introductions from Product Disposal

It is estimated that there will be no emissions to the environment from product disposal. As discussed in section 4.e., all product in the United States that is returned or rejected is completely destroyed by high-temperature incineration.

7. FATE OF SUBSTANCES IN THE ENVIRONMENT

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1 ppb.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1 ppb.

9. USE OF RESOURCES AND ENERGY

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1 ppb.

10. MITIGATION MEASURES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1 ppb.

11. ALTERNATIVES TO THE PROPOSED ACTION

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1 ppb.

12. LIST OF PREPARERS

This EA was prepared by:

Horace G. Rozier Jr.

- Environmental Engineer, Glaxo Wellcome Inc. 1993 - present
- Chemist, Ecoflo Inc. 1989-1993
- Chemist, Compuchem Environmental Corporation 1989
- Bachelor of Science in Biochemistry & Microbiology
  North Carolina State University , 1989

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Glaxo Wellcome Inc.

The undersigned official certifies that the EA summary document pages 1-5 contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR 1506.6.

Thomas F. Cecich
Vice President, Environmental Safety
Glaxo Wellcome Inc.

Oct. 31, 1996
Date

14. REFERENCES

Center for Drug Evaluation and Research, "Guidance For Industry For the Submission Of An Environmental Assessment In Human Drug Applications And Supplements," Federal Register, November 1995

Council On Environmental Quality, " Regulations On Implementing National Environmental Policy Act Procedures," Federal Register, Vol. 43, November 29, 1978, p. 55990.

Pharmaceutical Manufacturers Association, "Interim Guidance To The Pharmaceutical Industry For Environmental Assessment Compliance Requirements For The FDA v7," Seminar on Environmental Assessments, Rockville, Md., July 29-30, 1991.

U.S. FDA, "Environmental Assessment Technical Assistance Handbook", U.S. FDA, March 1987

U.S. FDA, "National Environmental Policy Act; Policies and Procedures; Final Rule," Federal Register, Vol. 50, April 26, 1985

15. APPENDIXES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be less than 1 ppb.

Wellcome

Burroughs Wellcome Co. Intersection U.S. 13 & S.R. 1590
Post Office Box 1887
Greenville, North Carolina 27835–1887

Cables & Telegrams
Tabloid Greenville, N.C.
TWX 5109291618
Tel. 919 758–3436

MATERIAL SAFETY DATA SHEET

GXSD/93/0002

SECTION I: IDENTIFICATION

Intermediate Name: VACC, VACD, VACG, VACH

Wellcome Registry # (Project #): 256U87 HCl (123)

Generic Name: Valacyclovir

CAS#: 124832–27–5

Chemical Name (IUPAC): 2–((2–Amino–1,6–dihydro–6–oxo–9*H*–purin–9–yl)methoxy)ethyl–*L*–valinate hydrochloride

Formula: $C_{13}H_{20}N_6O_4$ HCl

For Information on Health Hazards Call: Ext. 7014

Information Effective: 9/28/93

SECTION II: HAZARDOUS INGREDIENTS OF MIXTURES

Principal Component(s): Valacyclovir

Toxicity: Approximate lethal oral doses (LD_{50}):
Male and female rats: >5000 mg/kg.[1]
Female mice: >1000 mg/kg but <2000 mg/kg.[2]
Male mice: >2000 mg/kg.[2]

There were no signs of toxicity in monkeys given oral doses of valacyclovir at 125, 250, and 500 mg/kg/day for one year. Crystals, presumed to be acyclovir, were found occasionally in urine collected during the treatment period from mid and high dose monkeys. These crystals were not observed in urine samples collected during the recovery period.[3]

SECTION III: PHYSICAL DATA

Boiling Point: N.A.

Vapor Pressure: N.A.

Vapor Density: N.A.

Solubility in Water: 174 mg (anhydrous)/mL

Specific Gravity (H_2O=1): N.A.

Percent Volatile by Volume (%): N.A.

Evaporation Rate: N.A.

Melting Point: 219°C (I 3°C) with decomposition (anhydrite, form I)

Appearance and Odor: White to off white solid.

SECTION IV: FIRE AND EXPLOSION DATA

Flash Point (Method Used): N.D.

Flammable Limits: LEL: N.D. UEL: N.D.

Special Fire Fighting Procedures: Self-contained breathing apparatus

Unusual Fire and Explosion Hazards: May emit toxic or irritant fumes when heated.

Extinguishing Media: Use agent appropriate to the nature of the fire and other materials involved.

SECTION V: HEALTH HAZARD DATA

Routes of Exposure: Ingestion, inhalation, and possible absorption through eyes and skin.

Threshold Limit Value: None established.

Effects of Overexposure: In mice given lethal doses of valacyclovir, signs of overexposure were labored breathing, decreased body temperature, tremors, and decreased activity.[2] It was concluded that the kidney was the target organ for valacyclovir when given orally to the Cynomolgus Monkey at 400 and 600 mg/kg/day for 3 months.[4]

Emergency and First Aid Procedures:

If in Eyes: Flush immediately with large quantities of water. Contact Health Center.

If Swallowed: Do not induce vomiting. Have person drink water. Contact Health Center.

If Inhaled: Remove person to fresh air. Contact Health Center.

In Contact with Skin: Flush exposed skin with water and wash with soap and water. If irritation develops, contact Health Center.

SECTION VI: REACTIVITY DATA

Stability: N.D.

Incompatibility (Materials to Avoid): N.D.

Conditions to Avoid: N.D.

Hazardous Decomposition Products: N.D.

Hazardous Polymerization: N.D.

SECTION VII: SPILL OR LEAK PROCEDURES

Steps to be Taken if Material is Spilled or Leaked: Wear suitable protective clothing. Minimize dust generation. Wipe up with a wet cloth. Place in a closed container for disposal.

Waste Disposal Method: Contact Environmental Services for proper disposal procedures.

SECTION VIII: SPECIAL PROTECTION INFORMATION

Respiratory Protection:

Manufacturing Scale (>100 g): Toxic dust mask (e.g. 3M 8710).

Lab Scale (≤100 g): Toxic dust mask (e.g. 3M 8710) if dust is generated.

Ventilation: Fume hood or local exhaust.

Eye Protection: Goggles

Protective Gloves: Neoprene

Other Protective Equipment: Tyvek jumpsuit if dust is generated.

SECTION IX: SPECIAL PRECAUTIONS

Precautions to be Taken in Handling and Storage: Protect from heat and light.

Other Precautions: Wash hands after using.

SECTION X: REFERENCES

[1] An Acute Oral Toxicity Study in the Rat with BW 0256U87. Doc. No. TTEP/89/0003.

[2] An Acute Oral Toxicity Study (Limit Test) in the Mouse with BW 0256U87. Doc. No. TTEP/89/0007.

[3] A 52–Week Oral Toxicity Study of 256U87 in the Cynomolgus Monkey. Doc. No. TTEP/91/0043.

[4] A 90–Day Oral Toxicity Study of 256U87 in the Cynomolgus Monkey. Doc. No. TTEP/89/0034.

N.A. = Not Applicable
N.D. = Not Determined

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20550/S-003

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#:	20-550, SE1-003
APPLICANT:	Glaxo Wellcome Inc.
NAME OF DRUG:	Valtrex®
INDICATION:	Suppressive Therapy for Genital Herpes Simplex Virus Infections
DOCUMENTS REVIEWED:	Vol. 8.1-8.22,
CLINICAL REVIEWER:	HFD 530: Therese Cvetkovich, M.D.

A: Introduction

Two studies have been considered for the proposed new indication for suppression of recurrent genital herpes: 026 and 037. The drug has previously been approved for the treatment of both recurrent genital herpes and the initial episodes of genital herpes. "Recurrent" was defined as 8 or more episodes per year in 037 and 6 or more in 026. The presence and absence of a recurrence was evaluated at the end of six and twelve months of treatment. These evaluations have served as the primary focus of this review. Time-to-first recurrence was originally designated as the primary endpoint in the protocols, but has been viewed as secondary for the purpose of this review. The primary population was intent-to-treat which includes all patients randomized.

B: Study Design

Study 026

Protocol Title: "A Comparative Trial of Valaciclovir with Acyclovir and Placebo for the Suppression of Genital Herpes Infections in Immunocompetent Patients" (1/6/94)

This is an international, double-blind trial with both a placebo and active-control arms for examining the effects of valaciclovir (VACV) in the suppression of recurrent genital herpes. To be eligible, patients were to have six or more occurrences in the 12 months prior to study entry. Patients previously receiving suppressive aciclovir (ACV) therapy must have had one occurrence within three months of stopping therapy and within three months of starting the study. Approximately 1100 subjects were to be randomized to one of the following treatment arms:

VACV, 1000 mg once daily	200 patients
VACV, 500 mg once daily	200 patients
VACV, mg once daily	200 patients
VACV, mg twice daily	200 patients
ACV, 400 mg twice daily	200 patients
Placebo	100 patients

Each patient takes 3 pills in the morning and 2 pills in the evening.

Randomization was to be done with a block size 11 and a 2:2:2:2:2:1 treatment allocation at each center.

Each patient was to be treated for 52 weeks. Patients visited the clinics at monthly intervals and on days 1 and days 5 of a genital herpes recurrence. During a recurrence of genital herpes, patients were to be treated with VACV 500 mg bid. Once this open-label treatment was completed, the patient was to resume blinded study medication.

The primary efficacy analysis was to be based upon the time to first recurrence of genital herpes. The distribution of the time to first recurrence was to be estimated using the Kaplan-Meier product method. Tests of hypothesis were to be done using Cox regression of time-to-event controlling for prior Herpes Simplex Virus (HSV) history, type of study sites and number of patients enrolled at the study sites. If the assumption of proportional hazards was not supported by data then the analyses was to be based upon the proportion of patients recurrence free at six months and one year. Time to second recurrence of genital herpes was used as a secondary endpoint.

In Protocol Amendment #2 (1/18/96) it was specified that the testing will be conducted with a step down procedure in the following specified order:

(1) VACV, mg twice daily against placebo
(2) VACV, 1000 mg once daily against placebo
(3) VACV, 500 mg once daily against placebo
(4) VACV, mg once daily against placebo

The following strategy was to be used to select the dose:

If Test (1) is not significant then no dose is better than placebo.

If Test (1) is significant but (2) is not then VACV mg twice daily is the only effective VACV dose. It will then be compared with the ACV treatment arm.

If Test (1) and (2) are significant but (3) is not, then VACV 1000 mg once daily will be the only effective once daily dose. It will then be compared with VACV mg twice daily dose, if it significantly favors twice daily dose, then the mg twice daily dose will be compared with ACV treatment arm.

If Test (1), (2) and (3) are significant but not (4), then VACV 500 mg once daily will be the selected once daily dose. It will then be compared with VACV mg twice daily dose, if it significantly favors twice daily dose, then the mg twice daily dose will be compared with ACV treatment arm.

If Test (1)-(4) are all significant then dose response relation in the three once daily dose will be tested with a Cox regression model incorporating the treatment dose as a continuous covariate. If there is no dose response relation ($p >= 0.1$) then the VACV mg once daily will be selected. Otherwise the selection of doses will be based on analysis of hazard ratio. The selected once daily dose will then be compared with VACV mg twice daily dose, if it significantly favors twice daily dose, then th mg twice daily dose will be compared with ACV treatment arm.

The sample size of the protocol was based on the following assumptions:

For VACV treatment arms:

10% dropout rate,
60% patients recurrent-free in one year.
For ACV treatment arm:
10% dropout rate,
45% patients recurrent-free in one year.
For placebo patients:
5% recurrent-free in one year.
Power for comparing each VACV to ACV: 80%.
Power for comparing ACV to placebo: 80%.
Method of comparison: Cox proportional model for time to first recurrence.

Study 037

Protocol Title: "A Randomised, Double-Blind, Controlled Study of Valaciclovir for the Suppression of Recurrent Genital HSV Infection in Immunocompetent Patients" (9/9/94)

This is an international, double-blind, placebo-controlled trial for examining the drug effects in suppression of recurrent genital herpes. To be eligible, patients were to be averaging eight or more occurrences in the 12 months prior to study entry (assessed for at least 3 months). Or if the patient had been receiving HSV suppressive aciclovir therapy during the previous 12 months, the patient will need to have at least one recurrence of HSV infection within six weeks of discontinuing suppressive therapy and within 6 weeks preceding study entry. Approximately 262 subjects were to be randomized to one of the following treatment arms:

VACV, 500 mg once daily	198 patients
Placebo	66 patients

Randomization was to be done with a block size of 4 and a 3:1 treatment allocation stratified by center. Patients were to be treated for 16 weeks with open-label extension. Patients visited the clinic at 4-weekly intervals in the first 16 weeks and on days 1 and days 5 of a genital herpes recurrence. During the recurrence of the genital herpes patients were to be treated with VACV 500 mg bid. Once the open-label treatment was completed, the patient was to resume the study.

The primary efficacy analysis was to be based upon the time to first recurrence of genital herpes during the double-blind, randomized phase of the study. The distribution of the time to first recurrence will be estimated using the Kaplan-Meier product method. Tests of hypothesis were to be done using Cox regression of time-to-event controlling for prior HSV history and center. If the assumption of proportional hazards was not supported by data then the analyses were to be based upon the hazard ratios and the proportions of patients recurrence free at Week 12 through the relative statistics.

The intent-to-treat population was to be used for the primary efficacy analysis.

The sample size of the protocol was based on the following assumptions:
Hazard ratio >= 1.84 or <= 0.54,
10% dropout rate,
80% power,
Method of comparison: Cox proportional model for time to first recurrence.

C: Applicant's Results

Study 026

The study report is based upon subjects enrolled in 53 centers. The study period was from 4/94 to 1/96. 1479 patients were randomized into six treatment arms. The following table provides the distribution of subjects randomized by treatment and follow-up status for the full year (note, follow-up is higher in terms of the occurrence of one or more recurrences). There are no apparent differences among the active treatment arms (averaging 27% dropout rate) but patients withdrew at a markedly higher rate in the placebo group (46% dropout rate), especially during the first six months.

At the End of 12 Months

	VACV mg x 2	VACV 1000 mg x 1	VACV 500 mg x 1	VACV mg x 1	ACV 400 mg x 2	placebo
Total Randomized	274	269	266	269	267	134
Completed Protocol	202 (74%)	201 (75%)	194 (73%)	183 (68%)	197 (74%)	73 (54%)
Premature Discontinuation	72 (26%)	68 (25%)	72 (27%)	86 (32%)	70 (26%)	61 (46%)
AE	11	15	14	16	12	8
Inadequate Response*	6	5	2	16	4	23
Consent Withdrawn	19	22	25	24	25	11
Lost to Follow-up	30	19	25	23	24	15
Protocol Violation	6	7	6	7	5	4

Source: Tables 2 and 4, Vol. 5
* Typically the occurrences of 1 or more recurrences

The analyses were conducted for the intent-to-treat population which includes all patients randomized. In addition analyses for the primary endpoint were done for the efficacy subgroup which excludes patients with protocol deviation/violations. A total of 123 (8%) patients were excluded. The following table summarizes the distribution of patients in the two populations:

Number of Patients in Analysis Populations

	VACV mg x 2	VACV 1000 mg x 1	VACV 500 mg x 1	VACV mg x 1	ACV 400 mg x 2	placebo
Total Randomized	274	269	266	269	267	134
Intent-to-Treat	274	269	266	269	267	134
Efficacy Subgroup	249	245	246	243	249	124

Source: Table 15, Vol. 5

Baseline demographics and HSV history were similar across all six treatment groups (Source: Table 9,

10 of Vol. 5). 84% of the placebo patients had not participated in the previous clinical trials for VACV, which is slightly higher than percentages for actively treated groups which ranges from 78 - 80% (Source: Table 5, Vol. 5). Placebo patients had a slightly worse compliance record (Source: Table 8, Vol. 5). Among patients who received suppressive therapy in the previous year, fewer patients (39%) in the VACV 1000 mg once daily group and more patients in the ACV group (80%) experienced more than 9 recurrences per year compared to the other treatment groups (percentages ranged from 50% to 68%) (Source: Table 11, Vol. 5).

1) Crude Proportion of Patients Recurrence Free at 6 Months

The table below summarizes the patient disposition at the end of six months trial with respect to treatment status:

At the End of Six Months

	VACV mg x 2	VACV 1000 mg x 1	VACV 500 mg x 1	VACV mg x 1	ACV 400 mg x 2	placebo
Total Randomized	274	269	266	269	267	134
Completed Protocol	224 (82%)	226 (84%)	222 (83%)	208 (77%)	224 (84%)	85 (63%)
Premature Discontinuation	50 (18%)	43 (16%)	44 (17%)	61 (23%)	43 (16%)	49 (37%)

Source: Tables 2, Vol. 5

The table below summarizes the status of the patients after 180 days in the trial with respect to recurrences. Patients are classified as either recurrence free, recurrence occurring, or of unknown status due to loss to follow-up:

Patient Status at the End of Six Months

Treatment Group	Overall			HSV Rec. History <= 9			HSV Rec. History > 9		
6 months =180 days	# of Pts	# Rec. Free (%)	# un-knwn(%)	# of Pts	# Rec. Free (%)	# un-known(%)	# of Pts	# Rec. Free (%)	# un-known(%)
VACV x 2	274	147 (53.6)	36 (13.1)	144	91 (63.2)	19 (13.2)	130	56 (43.1)	17 (13.1)
VACV 1000 x 1	269	148 (55.0)	27 (10.0)	148	84 (56.8)	16 (10.8)	121	64 (52.9)	11 (9.1)
VACV 500 x 1	266	123 (46.2)	27 (10.2)	174	90 (51.7)	17 (9.8)	92	33 (35.9)	10 (10.9)
VACV x 1	269	70 (26.0)	35 (13.0)	157	44 (28.0)	29 (18.5)	112	26 (23.2)	6 (5.4)
ACV 400 x 2	267	144 (53.9)	27 (10.1)	136	77 (56.6)	15 (11.0)	131	67 (51.1)	12 (9.2)
Placebo	134	9 (6.7)	14 (10.4)	69	5 (7.2)	7 (10.1)	65	4 (6.2)	7 (10.8)

Source: Table 29 of Vol. 5

The percentage of patients with unknown status (patients withdrew before any recurrence before 180 days) varied from 10% to 13%. These patients were assumed to have a recurrence in the primary analysis. Center-stratified Cochran-Mantel-Haenszel (CMH) analyses of these proportions are summarized below:

Intent-to-Treat Analysis

Comparisons	Risk Ratio	95% CI	p-value
VACV mg x 2 *vs.* Placebo	0.456	(0.387, 0.537)	<0.001
VACV 1000 mg x 1 *vs.* Placebo	0.468	(0.398, 0.551)	<0.001
VACV 500 mg x 1 *vs.* Placebo	0.545	(0.469, 0.634)	<0.001
VACV mg x 1 *vs.* Placebo	0.777	(0.695, 0.868)	0.003
VACV 1000 mg x 1 *vs.* VACV 500 mg x 1	0.836	(0.701, 0.998)	*
ACV 400 mg x 2 *vs.* Placebo	0.469	(0.397, 0.554)	*
VACV mg x 2 *vs.* VACV 1000 mg x 1	1.019	(0.845, 1.228)	0.846
VACV ...g x 2 *vs.* ACV 400 mg x 2	0.992	(0.823, 1.196)	*

Source: Table 7 of Glaxo response to FDA
*: These comparisons were not specified in the protocol

All VACV containing treatments are effective in suppressing recurrent genital herpes compared to placebo at significance level 0.05, after adjusting for 4 multiple comparisons.

FDA requested sensitivity analysis of the crude proportion of patients recurrence free at 6 months in order to investigate the robustness of this analysis. The following table compares the crude proportion of patients recurrence free at 6 months using the various methods of handling patients who withdrew before 6 months without any recurrences (Success is defined as recurrence free in the first 180 days):

6 months = 180 Days	VACV mg x 2	VACV 1000 mg x 1	VACV 500 mg x 1	VACV mg x 1	ACV 400 mg x 2	Placebo
All unknowns as failures	54%	55%	46%	26%	54%	7%
Unknowns before 90 days as failures; otherwise successes	56%	57%	48%	28%	57%	7%
All unknowns as successes	67%	65%	56%	39%	64%	17%
All unknowns excluded	62%	61%	52%	30%	60%	8%

Source: Table 1 of Glaxo response to FDA

All the comparisons for VACV containing treatments vs. Placebo by Center-stratified CMH analyses yielded p-values < 0.001, statistically significant at level 0.0125 = 0.05/4 with adjustment for 4 multiple comparisons.

2) Crude Proportion of Patients Recurrence Free at 12 Months

The table below summarizes the status of the patients after 360 days in the trial:

Patient Status at the End of Twelve Months

Treatment Group	Overall			HSV Rec. History <= 9			HSV Rec. History > 9		
12 months=360days	# of Pts	# Rec. Free	%	# of Pts	# Rec. Free	%	# of Pts	# Rec. Free	%
VACV x 2	274	94	34.3	144	60	41.7	130	34	26.2
VACV 1000 x 1	269	92	34.2	148	53	35.8	121	39	32.2
VACV 500 x 1	266	75	28.2	174	54	31.0	92	21	22.8
VAC\ x 1	269	40	14.9	157	25	15.9	112	15	13.4
ACV 400 x 2	267	92	34.5	136	47	34.6	131	45	34.4
Placebo	134	6	4.5	69	2	2.9	65	4	6.2

Source: Table 29 of Vol. 5

The percentage of patients with unknown status (patients withdrew before the completion of the study) varied from 10% (Placebo group) to 22% (VACV x 2) (Source: Table 29 and 33 of Vol. 5). These patients were assumed to have a recurrence in the analysis. Center-stratified CMH analyses of these proportions are summarized below:

Intent-to-Treat Analysis

Comparisons	Risk Ratio	95% CI	p-value
VACV: mg x 2 *vs.* placebo	0.629	(0.551, 0.719)	<0.001
VACV 1000 mg x 1 *vs.* placebo	0.650	(0.572, 0.739)	<0.001
VACV 500 mg x 1 *vs.* placebo	0.690	(0.604, 0.787)	<0.001
VAC\ mg x 1 *vs.* placebo	0.841	(0.752, 0.942)	0.003
VACV 1000 mg x 1 *vs.* VACV 500 mg x 1	0.909	(0.803, 1.029)	*
ACV 400 mg x 2 *vs.* placebo	0.641	(0.561, 0.732)	*
VACV mg x 2 *vs.* VACV 1000 mg x 1	0.999	(0.875, 1.140)	0.987
VAC mg x 2 *vs.* ACV 400 mg x 2	0.996	(0.872, 1.138)	*

Source: Table 30 of Vol. 5

*: These comparisons were not specified in the protocol

The conclusion was identical to the six month analysis: all VACV containing treatments are efficacious when compared to placebo.

FDA requested sensitivity analysis of the crude proportion of patients recurrence free at 12 months in order to investigate the robustness of this analysis. The following table compares the crude proportion of patients recurrence free at 12 months using the various different methods for handling patients who

withdrew before 12 months without having a recurrence (Success is defined as 12 months recurrence free):

12 months = 360 Days	VACV mg x 2	VACV 1000 mg x 1	VACV 500 mg x 1	VACV mg x 1	ACV 400 mg x 2	Placebo
All unknowns as failures	34%	34%	28%	15%	34%	4%
Unknowns before 270 days as failures; otherwise successes	41%	41%	33%	18%	42%	4%
Unknowns before 180 days as failures; otherwise successes	43%	43%	36%	19%	43%	4%
Unknowns before 90 days as failures; otherwise successes	46%	45%	38%	20%	46%	4%
All unknowns as successes	56%	54%	46%	32%	54%	15%
All unknowns excluded	44%	42%	34%	18%	43%	5%

Source: Table 9-16, Vol. 15

The statistical tests again showed that VACV containing treatments are superior to placebo.

3) Time to First Recurrence

Time to first recurrence was defined to be the number of days from last screen date to first date of onset of lesions. For patients who did not have any recurrences, censored event-free times were calculated to be equal to the last day that the patient was known to be recurrence free. The following table summarizes the number of patients with/without a recurrence for the intent-to-treat and efficacy populations.

	VACV mg x 2	VACV 1000 mg x 1	VACV 500 mg x 1	VACV mg x 1	ACV 400 mg x 2	placebo
Total Randomized	274	269	266	269	267	134
Intent-to-Treat	274	269	266	269	267	134
Number with an Event	121	130	145	185	124	114
Number Censored	153	139	121	84	143	20
Efficacy Subgroup	249	245	246	243	249	124
Number with an Event	104	112	133	168	114	105
Number Censored	145	133	113	75	135	19

Source: Table 16, 19 Vol. 5

The primary analyses for this endpoint was the intent-to-treat population analyses. Efficacy subgroup analyses were performed as supportive analyses. Cox's proportional hazards model was used to estimate the treatment differences. The basic model adjusted for center (all small centers were combined into one large center) and HSV recurrence history (> 9 recurrences per year *vs.* <= 9 per year). The results for

intent-to-treat population are summarized in the following table:

Intent-to-Treat Analysis

Comparisons	Hazard Ratio	95% CI	p-value
VACV mg x 2 *vs.* Placebo	0.210	(0.161, 0.274)	<0.0001
VACV 1000 mg x 1 *vs.* placebo	0.222	(0.171, 0.287)	<0.0001
VACV 500 mg x 1 *vs.* placebo	0.286	(0.221, 0.369)	<0.0001
VAC mg x 1 *vs.* placebo	0.463	(0.364, 0.590)	<0.0001
Linear trend for 250 mg, 500 mg, 1000 mg once daily dose	N/A	N/A	<0.0001
VACV 1000 mg x 1 *vs.* VACV 500 mg x 1	0.776	(0.611, 0.985)	*
ACV 400 mg x 2 *vs.* placebo	0.209	(0.160, 0.271)	*
VACV mg x 2 *vs.* VACV 1000 mg x 1	0.948	(0.739, 1.216)	0.676
VAC mg x 2 *vs.* ACV 400 mg x 2	1.007	(0.783, 1.296)	*
HSV Recurrence History <= 9 *vs.* > 9	0.749	(0.648, 0.865)	p < 0.0001

Source: Table 18 of Vol. 5
*: These comparisons were not specified in the protocol

According to the step down testing procedure specified in the protocol, all the four VACV treatments are efficacious. The hazard ratio indicated a consistent trend in increasing efficacy with increasing doses for once daily VACV treatment, and the hypothesis test of whether a dose response was present across the three once daily VACV groups was significant, therefore VACV 1000 mg once daily was the most efficacious once daily dose. The comparison of VACV 1000 mg once daily against VACV mg twice daily was not statistically significant. The Analyses for efficacy subgroup gave very similar results (Source: Table 21, Vol. 5).

FDA requested an analysis of time to first recurrence stratified only by stratification variables for randomization (i.e., center) (2/27/96). The estimated hazards ratios and 95% CIs were almost identical (Source: Table 1 and 2 of Vol. 15) to the table above.

The analysis reaffirmed the conclusion that all VACV containing treatments are superior to placebo.

Subgroup Analysis : ≤ 9 recurrences and > 9 recurrences at baseline

As observed in the above table, the recurrence free rate was higher for patients experiencing 9 or less recurrences per year when not receiving suppressive therapy than patients experiencing 9 or more recurrences per year. The following table summarizes the number of patients recurrence free in each treatment group for each HSV recurrence history subgroup.

Dosing Regimens	Kaplan-Meier Proportion of patients recurrence free at 12 months (360 days) (%)	
	<= 9 HSV recurrences per year	> 9 HSV recurrences per year
VACV mg x 2	59	40
VACV 1000 mg x 1	50	47
VACV 500 mg x 1	46	30
VACV ng x 1	27	16
ACV 400 mg x 2	53	45
placebo	3	8

Source: Table 24 and 25 of Vol. 5

The following tables summarizes the analyses results for each HSV recurrence history subgroup.

Comparisons	HSV Recurrence history <= 9		HSV Recurrence history > 9	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
VACV . ng x 2 *vs.* placebo	0.122	(0.083, 0.181)	0.325	(0.226, 0.468)
VACV 1000 mg x 1 *vs.* placebo	0.160	(0.110, 0.231)	0.274	(0.188, 0.400)
VACV 500 mg x 1 *vs.* placebo	0.182	(0.128, 0.258)	0.451	(0.308, 0.659)
VACV ng x 1 *vs.* placebo	0.319	(0.227, 0.448)	0.632	(0.446, 0.895)
ACV 400 mg x 2 *vs.* placebo	0.160	(0.109, 0.234)	0.261	(0.181, 0.378)

Source: Table 26 and 27 of Vol. 5

It appears that patients with ≤ 9 recurrences per year responded to the VACV therapy better than those with > 9 recurrences per year, even though VACV x 2, VACV 500 x 1 and VACV 1000 x 1 seemed to be efficacious in both subgroups. It also appears that the differences between the two subgroups were larger in VACV x 2 and VACV 500 x 1 than in VACV 1000 x 1. Further analyses will be presented in the Reviewer's Comments section later.

HSV history, Gender, Previous suppression (Yes or No) and Time from episode (>= 5 years *vs.* < 5 years) were added to the basic Cox regression model as covariates in order to investigate if they were prognostic factors. The results were summarized in the following table:

Covariate	Hazard Ratio	95% CI
Gender (Male *vs.* Female)	0.695	(0.600, 0.865)
Previous Suppression (No *vs.* Yes)	0.867	(0.712, 1.052)
Time from First Episode (>= 5 years *vs.* < 5 years)	0.911	(0.789, 1.052)

It appeared that males responded better than females. However, no subgroup analysis was done by the sponsor to further investigate this difference. This analysis will be presented in the Reviewer's

Comments section.

4) Time to Second Recurrence

The Kaplan-Meier proportion of patients who were free of a second recurrence at 12 months (360 days) was 75% for the valaciclovir mg x 2 and ACV groups, dropping to 68% for VACV 1000 mg x 1, 65% for VACV 500 mg x 1, 44% for VACV mg x 1, and 14% fore placebo patients.

The results of the basic Cox regression is summarized below, the conclusion is similar to those of the time-to-first-recurrence analysis.

Intent-to-Treat Analysis

Comparisons	Hazard Ratio	95 CI
VACV mg x 2 *vs.* placebo	0.117	(0.084, 0.164)
VACV 1000 mg x 1 *vs.* placebo	0.149	(0.109, 0.204)
VACV 500 mg x 1 *vs.* placebo	0.182	(0.133, 0.248)
VACV mg x 1 *vs.* placebo	0.328	(0.249, 0.434)
VACV 1000 mg x 1 *vs.* VACV 500 mg x 1	0.819	(0.598, 1.122)
ACV 400 mg x 2 *vs.* placebo	0.108	(0.077, 0.152)
VACV ng x 2 *vs.* VACV 1000 mg x 1	0.786	(0.560, 1.105)
VACV mg x 2 *vs.* ACV 400 mg x 2	1.082	(0.754, 1.554)

Source: Table 34 of Vol. 5

Study 037

The study report is based upon subjects enrolled in 34 centers. The study period was from December 1994 to August 1995. A total of 382 patients were randomized into 2 treatment groups, with 288 in the VACV 500 mg once daily group and 94 in the placebo group. The dropout rates were very low compared to Study 026 — 7% in the VACV arm and 2% in the placebo arm. This is most likely due to the short trial period (12 weeks for Study 037 vs. 12 months for Study 026) and different definitions of completion: all patients with a recurrence in the 16 weeks double-blind period were considered completers in Study 037 while the patients had to stay in the double-blind study for one year regardless if the patients have had recurrences before the end of study in Study 026 (Source: Table 4, Vol. 16). Of these dropouts, 7 were due to AEs and all of them occurred in VACV group.

The primary endpoint for this study is time to first recurrence. The analysis populations were the same as in the Study 026. They include the intent-to treat population and the efficacy subgroup which excludes patients with protocol deviation/violation. A total of 46 patients (12%) patients were excluded. 39 were from the VACV treatment group (13.5%) and 7 were from the placebo group (7.4%). The following table summarizes the distribution of patients in the two populations:

	VACV 500 mg x 1	placebo
Total Randomized	288	94
Intent-to-Treat	288	94
Efficacy Subgroup	249	87

Source: Table 14, Vol. 16

Time to First Recurrence

The following table summarizes the number of patients with/without a recurrence for the two aforementioned populations:

	VACV 500 mg x 1	placebo
Total Randomized	288	94
Intent-to-Treat	288	94
Number with an Event	87	83
Number Censored	201	11
Efficacy Subgroup	249	87
Number with an Event	72	78
Number Censored	177	9

Source: Table 15, 18 Vol. 16

The primary analyses for this trial was the intent-to-treat population analyses. Efficacy subgroup analyses were performed as supportive analyses. Cox's proportional hazards model was used to estimate the treatment differences. The basic model adjusted for center (all small centers were combined into one large center) and HSV recurrence history (> 9 recurrences per year vs. 9 per year). The results are summarized in the following tables:

Population	Comparisons	Hazard Ratio	95% CI	p-value
Intent-to-treat	VACV 500 mg x 1 *vs.* placebo	0.155	(0.112, 0.214)	<0.0001
	HSV Recurrence History = 9 *vs.* > 9	0.684	(0.493, 0.951)	0.0237
Efficacy Subgroup	VACV 500 mg x 1 *vs.* placebo	0.139	(0.098, 0.198)	<0.0001
	HSV Recurrence History = 9 *vs.* > 9	0.661	(0.462, 0.946)	0.0235

Source: Table 17 and 20 of Vol. 16

The treatment effects depends on the HSV recurrence history. The following table summarizes the analyses for each HSV recurrence history subgroup.

Comparisons	HSV Recurrence history = 9		HSV Recurrence history > 9	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
VACV 500 mg x 1 *vs.* placebo	0.178	(0.107, 0.297)	0.132	(0.083, 0.209)

Source: Table 22 of Vol. 16

Each prognostic factor was added into the basic model on its own as a covariate to see if its association with the time to first recurrence is statistically significant. If significant, it was selected into the 'final' model. The prognostic factor investigated include Gender, Age (< 34 years, >= 34 years), Previous Suppression (Yes or No) and Time from Primary Episode (< 5 years, >= 5 years). The final model is the basic model with Time from Primary Episode as additional covariate. The estimated treatment difference and associated p-values changed little from the basic model. The results are summarized below:

Population	Comparisons	Hazard Ratio	95% CI	p-value
Intent-to-treat	VACV 500 mg x 1 *vs.* placebo	0.149	(0.108, 0.206)	<0.0001
	HSV Recurrence History = 9 *vs.* > 9	0.716	(0.514, 0.996)	0.0473
	Time From Primary Episode < 5 *vs.* >= 5 years	0.718	(0.514, 1.003)	0.0519

Source: Table 21 of Vol. 16

D: Reviewer's Comments

1) Multiple Comparison Adjustment

A statistical review was conducted by FDA for the step-down procedure proposed by the sponsor in Study 026. Reservations were expressed as to the suitability of this procedure. This issue was not resolved prior to the submission of the NDA. For the purpose of this review, a Bonferoni adjustment of 0.05/4 has been used for evaluating VACV doses versus placebo.

2) Efficacy

Study 026

VACV 250 mg bid, 1000 mg qd, 500 mg qd and mg qd are all efficacious when compared to placebo. The sponsor used different imputation methods for dropouts but the statistical tests for the crude proportions at 6 and 12 months are all significant at 0.05/4 = 0.0125. The primary analysis, where all dropouts were classified as failures, was least favorable to the sponsor.

All the sponsor's imputation methods classified dropouts with rules common to all the treatment groups. For crude proportions, a very conservative analysis would be to assume all dropouts as successes (recurrence free) for placebo treated patients and failures for VACV treated patients. In this case the comparisons to placebo by using an asymptotically normal test (Z-test) without adjusting for center effects (Note, center adjustment using CMH were conducted for this review and were consistent with the unadjusted analysis. For simplicity, only the unadjusted analyses are presented) give the following results:

Treatment Group	End of six months			End of 12 months		
	Rec. free (%)	Diff. Vs. Pbo (%)	p-value	Rec. free (%)	Diff. vs. Pbo (%)	p-value
VACV x 2	54♦	36	<0.0001*	34♦	19	<0.0001*
VACV 1000 x 1	55♦	38	<0.0001*	34♦	19	<0.0001*
VACV 500 x 1	46♦	29	<0.0001*	28♦	13	0.0013*
VACV x 1	26♦	9	0.0356	15♦	-0	1
ACV 400 x 2	54♦	37	<0.0001*	34♦	20	<0.0001*
Placebo	170			150		

◊: All dropouts are treated as recurrence free
♦: All dropouts are treated as failures
*: Statistically significant at 0.0125

This shows the overall superiority of the VAC mg bid, 1000 mg qd and 500 mg qd over placebo, and this conclusion is not affected by how patients who dropped out before any HSV recurrence are dealt with. On the other hand, the comparison of VAC mg qd to placebo is sensitive to such assumptions and as we can see from the table above, certain classification methods will lead to the conclusion that there is no apparent difference between VAC mg qd and placebo.

Study 037

Study 037 is only 16 weeks long and the crude proportions analysis was not contained in the submission. The following table summarizes the patient status after 16 weeks treatment:

Patient Status at the End of 16 weeks: Study 037

Treatment Group	Overall			HSV Rec. History <= 9			HSV Rec. History > 9		
16 weeks = 102 days	# of Pts	# Rec. Free (%)	# un-knwn(%)	# of Pts	# Rec. Free (%)	# un-known(%)	# of Pts	# Rec. Free (%)	# un-known(%)
VACV 500 x 1	288	183 (63.5)	22 (7.6)	138	90 (65.2)	13 (9.4)	150	93 (62.0)	9 (6.0)
Placebo	94	9 (9.6)	3 (3.2)	44	6 (13.6)	2 (4.5)	50	3 (6.0)	1 (2.0)

Similar to the above analysis for Study 026, if the unknowns are classified as recurrence free in the placebo group and as failures in the VACV 500 mg qd treated group, the statistical test for the difference between the crude proportions in the two arms yielded p-value < 0.001 overall and for each of the subgroup defined by HSV recurrent history (≤9 vs. > 9 recurrences/year). This shows that VACV 500 mg qd is efficacious in suppressing recurrent genital herpes in 16 weeks compared to placebo.

3) Gender

Study 026

The sponsor examined the effects of gender on the time to first recurrence and found it to be a significant modifier of the treatment effects. Since the primary efficacy measures for this review are the recurrence free rates at the end of six and twelve months, it is important to confirm this conclusion with respect to these two measures.

The recurrence free rates for females and males are summarized in the following table:

Recurrence free rates at the end of 6 months

Treatment Group	Overall			Female			Male		
	# of Pts	Rec. Free (%)	unknown (%)	# of Pts	Rec. Free (%)	unknown (%)	# of Pts	Rec. Free (%)	unknown (%)
VACV x 2	274	53.6	13.1	143	47.6	18.2	131	60.3	7.6
VACV 1000 x 1	269	55.0	10.0	137	46.0	11.0	132	64.4	9.1
VACV 500 x 1	266	46.2	10.2	143	42.0	11.2	123	51.2	8.9
VACV x 1	269	26.0	13.0	127	21.3	14.2	142	30.3	12.0
ACV 400 x 2	267	53.9	10.1	141	45.4	10.6	126	63.5	9.5
Placebo	134	6.7	10.4	79	6.3	13.9	55	7.3	5.5

Recurrence free rates at the end of 12 months

Treatment Group	Overall			Female			Male		
	# of Pts	Rec. Free (%)	unknown (%)	# of Pts	Rec. Free (%)	unknown (%)	# of Pts	Rec. Free (%)	unknown (%)
VACV x 2	274	34.3	21.9	143	26.6	26.6	131	42.6	16.8
VACV 1000 x 1	269	34.2	19.3	137	24.1	19.7	132	44.7	18.9
VACV 500 x 1	266	28.2	17.7	143	25.2	17.5	123	31.7	17.9
VACV x 1	269	14.9	16.7	127	12.6	17.3	142	16.9	16.2
ACV 400 x 2	267	34.5	19.1	141	28.4	13.5	126	41.3	25.4
Placebo	134	4.5	10.5	79	3.8	13.9	55	5.5	5.5

From these two tables we see that males responded better than females for the active arms. Males and females are comparable in placebo. The CMH test controlling for treatment showed that the recurrence free rates in males and females differ ($p<0.001$) at both 6 and 12 months. The CMH test for the differences in male and female recurrence free rates for each treatment group yielded the following results:

p-values for the difference between male and female recurrence free rates

Treatment	VACV x 2	VACV 1000	VACV 500	VACV	ACV 400 x 2	Pbo
6 months	0.035	0.002	0.132	0.093	0.003	0.831
12 months	0.005	0.001	0.239	0.323	0.027	0.649

This shows that there are differences between males and females in the recurrence free rates at the end of six and twelve months in VACV mg bid, VACV 1000 mg qd and ACV 400 mg bid treated patients.

Study 037

The sponsor's results indicated that gender is not a significant modifier of the treatment effects for VACV 500 mg qd in this study (p-value = 0.8028). The Week 16 analysis for Study 026 showed that VACV 500 mg qd had recurrence free rates of 52.4% and 67.5% in females and males respectively, statistically significant at level 0.05 (p-value = 0.0114). Examining the Kaplan-Meier plots of the

recurrence free rates for the two studies (page 317, Vol. 5 and page 129, Vol. 16) supported these different conclusions. Note however that the difference in Study 026 appears to moderate over time.

4) Dose Selection

Study 026

The prognostic factors investigated in the submission included HSV recurrent history, Gender, Age (< 34, ≥ 34), Previous Suppression (Yes, No) and Time from primary episode (< 5 vs. ≥ 5 years). Among them HSV recurrent history was pre-specified in the protocol as a covariate in the Cox regression analysis for time to first recurrence. The sponsor's analysis showed that both HSV recurrence history and gender affected the time to first recurrence. This analysis does not address whether the treatment effect varies by subgroups, but only whether or not the rate changes by subgroup.

The following table summarizes the overall recurrence free rates and the rates in subgroups defined by HSV recurrent history and gender at 6 and 12 months:

Proportion of Patients Recurrence Free
All unknowns are classified as failures

Treatment Group	6 months					12 months				
	overall	≤9 rec./year	>9 rec./year	Female	Male	overall	≤9 rec./year	>9 rec./year	Female	Male
VAC x 2	53.6	63.2	43.1	47.6	60.3	34.3	41.7	26.2	26.6	42.6
VACV 1000 x 1	55.0	56.8	52.9	46.0	64.4	34.2	35.8	32.2	24.1	44.7
VACV 500 x 1	46.2	51.7	35.9	42.0	51.2	28.2	31.0	22.8	25.2	31.7
VACV x 1	26.0	28.0	23.2	21.3	30.3	14.9	15.9	13.4	12.6	16.9
ACV 400 x 2	53.9	56.6	51.1	45.4	63.5	34.5	34.6	34.4	28.4	41.3
Placebo	6.7	7.2	6.2	6.3	7.3	4.5	2.9	6.2	3.8	5.5

To aid the selection of VACV doses, comparisons will be conducted among VACV doses with the goal of eliminating inferior doses. Further analysis will be conducted in subgroups defined by HSV recurrent history and gender to fine tune the selection.

From the table above we see that the VACV mg qd dose had the lowest recurrence free rate among all VACV doses in the study 026. It is inferior to the other three VACV doses ($p < 0.0002$) in overall recurrence free rates in both the six month and 12 month analyses. The same conclusion holds in all the subgroups defined by HSV recurrent history and gender ($p < 0.001$). Therefore this dose will not be considered further.

Of the remaining three VACV doses, VACV 500 mg qd appears to be least efficacious. The statistical comparisons of the overall recurrence free rates for VACV mg bid and VACV 1000 mg qd vs. VACV 500 mg qd yielded p-values of 0.0843 and 0.0415 at the end of six months and 0.1246 and 0.1330 at the end of twelve months, respectively, providing evidence that VACV mg bid and VACV 1000 mg qd may be better than VACV 500 mg qd. The following table summarizes similar analyses for pairwise comparisons among VACV bid, 1000 mg qd and 500 mg qd at the end of six and twelve months. The analyses are extended to the HSV history and gender subgroups.

Relative difference in recurrence free rates
All unknowns are treated as failures

Comparisons	Sub-group	6 months			12 months		
		Diff	95% CI	p-value	Diff	95% CI	p-value
VACV x2 vs. 1000 x1	Overall	-0.0137	-0.097, 0.070	0.7488	0.0011	-0.079, 0.081	0.9793
	≤9 rec.	0.0644	-0.048, 0.177	0.2605	0.0586	-0.053, 0.170	0.3037
	>9 rec.	-0.0982	-0.221, 0.025	0.1181	-0.0608	-0.173, 0.052	0.2894
	Female	0.0157	-0.101, 0.133	0.7927	0.0249	-0.077, 0.127	0.6323
	Male	-0.0409	-0.158, 0.076	0.4934	-0.0195	-0.139, 0.100	0.7500
VACV x2 vs. 500 x1	Overall	0.0741	-0.010, 0.158	0.0843	0.0611	-0.017, 0.139	0.1246
	≤9 rec.	0.1147	0.006, 0.223	0.0378	0.1063	+0, 0.212	0.0490
	>9 rec.	0.0721	-0.058, 0.202	0.2765	0.0333	-0.081, 0.148	0.5682
	Female	0.0559	-0.059, 0.171	0.3407	0.0140	-0.088, 0.115	0.7871
	Male	0.0909	-0.031, 0.213	0.1436	0.1104	-0.008, 0.228	0.0668
VACV 1000 x1 vs. 500 x1	Overall	0.0878	0.003, 0.172	0.0415	0.0601	-0.018, 0.138	0.1330
	≤9 rec.	0.0503	-0.059, 0.159	0.3655	0.0478	-0.056, 0.151	0.3652
	>9 rec.	0.1702	0.038, 0.303	0.0117	0.0941	-0.025, 0.214	0.1231
	Female	0.0403	-0.076, 0.156	0.4970	-0.0109	-0.111, 0.090	0.8328
	Male	0.1317	0.011, 0.252	0.0319	0.1299	0.012, 0.248	0.0312

Even though the overall recurrence free rates appear to favor VACV mg bid and 1000 mg qd over 500 mg qd, the patterns in subgroups are more complicated. Among patients with 9 or fewer recurrences, the recurrence free rates for VACV 1000 mg qd and VACV 500 mg qd treated were 56.8% and 51.7% respectively in the first 6 months, yielding a relatively small treatment difference of 5.0% which is not statistically significant (p=0.366). On the other hand, the rates of 52.9% and 35.9% for patients with 10 or more recurrences per year give a relative large treatment difference of 17.0%, statistically significant (p=0.0117) at level 0.05. It appears that the relative treatment differences between VACV 1000 mg qd and 500 mg qd differ in the two HSV history subgroups (i.e., interaction). To understand if such a difference is merely due to chance, a Z-test for the difference (observed to be 12.0% = 17% - 5.1%) of the two relative treatment differences (i.e., test of interaction) was conducted and it yielded a two-sided p-value of 0.1705. Therefore it has not been shown that the relative treatment differences differ in the HSV history subgroups for VACV 1000 mg qd and 500 mg qd. Interaction tests for other pairs of treatments by HSV recurrent history and gender were similarly examined and the results are summarized below:

Interaction between treatment and HSV recurrent history
All unknowns are treated as failures

Treatments Compared	Crude proportions at 6 months		Crude proportions at 12 months	
	95% CI for the diff. of rel. eff.	Two-sided P-value	95% CI for the diff. of rel. eff.	Two-sided P-value
VACV mg bid vs. VACV 1000 mg qd	(-0.004, 0.329)	0.056	(-0.039, 0.278)	0.140
VACV mg bid vs. VACV 500 mg qd	(-0.126, 0.212)	0.621	(-0.083, 0.229)	0.358
VACV 1000 mg qd vs. VACV 500 mg qd	(-0.291, 0.052)	0.170	(-0.204, 0.112)	0.566

Interaction between treatment and gender
All unknowns are treated as failures

Treatments Compared	Crude proportions at 6 months		Crude proportions at 12 months	
	95% CI for the diff. of rel. eff.	Two-sided P-value	95% CI for the diff. of rel. eff.	Two-sided P-value
VACV mg bid vs. VACV 1000 mg qd	(-0.109, 0.222)	0.503	(-0.113, 0.202)	0.581
VACV mg bid vs. VACV 500 mg qd	(-0.202, 0.133)	0.683	(-0.252, 0.059)	0.225
VACV 1000 mg qd vs. VACV 500 mg qd	(-0.259, 0.076)	0.284	(-0.296, 0.015)	0.076

The 12 months analysis confirmed that there is not sufficient evidence to show that the relative treatment differences between VACV 1000 mg qd and 500 mg qd (p=0.566) differ in the two HSV history subgroups.

The interaction of VACV 1000 mg qd and VACV 500 mg qd by gender is nearly statistically significant (p=0.076) at the end of 12 months. However, six months data is less supportive (p=0.284). For males, the 95% confidence intervals for the treatment differences of VACV 1000 mg qd and 500 mg qd at the end of six and twelve months are (0.011, 0.252) and (0.012, 0.248) respectively, indicating that VACV 1000 mg qd may be a better treatment. For females, the treatment differences between the two doses are small at both 6 months and 12 months. The weak evidence of interaction does not lend strong support for selecting different doses between VACV1000 mg qd and 500 mg qd in the two gender subgroups.

The interactions of VACV mg bid and VACV 500 mg qd by HSV recurrent history and by gender were not shown to be statistically significant. Therefore the comparison of these two doses should be primarily based upon the overall recurrence free rates. The 95% confidence intervals for the difference of the recurrence free rates for these two doses at the end of six months and 12 months were (-0.010, 0.158) and (-0.017, 0.139) respectively, showing marginal evidence that VACV mg bid is superior to VACV 500 mg qd.

The comparison of VACV mg bid vs. VACV 1000 mg qd by HSV recurrent history interaction is nearly statistically significant at 0.05 (p=0.056) at the end of six months. 12 months data is supportive of this finding (p=0.140). For patients with 9 or fewer recurrences, it appears that VACV mg bid is a better treatment than VACV 1000 mg qd. While for patients with 10 or more recurrences per year, 1000 mg qd appears to be better.

Study 037

The treatment effect size for VACV 500 mg qd, as measured by the difference of the recurrence free rates for VACV 500 mg qd and placebo, were 51.6% among patients with 9 or few recurrences per year and 56.0% among patients with 10 or more recurrences per year. To see if VACV 500 mg qd is equally efficacious in these two subgroups, a statistical test was conducted without adjusting for the center effects for the difference in the effect size (observed to be -4.4% = 51.6% - 56.0%) and the test yielded p-value of 0.598 and 95% confidence interval of (-0.208, 0.120). Therefore we have little evidence that treatment effects of VACV 500 mg qd differ in the two HSV recurrent history subgroups. To make the two studies comparable, the recurrence free rates at Week 16 are summarized below for Study 026:

Patient Status at the End of 16 weeks: Study 026

Treatment Group	Overall			HSV Rec. History <= 9			HSV Rec. History > 9		
16 weeks =102 days	# of Pts	# Rec. Free (%)	# un-knwn(%)	# of Pts	# Rec. Free (%)	# un-known(%)	# of Pts	# Rec. Free (%)	# un-known(%)
VACV x 2	274	172 (62.8)	32 (11.7)	144	102 (70.8)	17 (11.8)	130	70 (53.9)	15 (11.5)
VACV 1000 x 1	269	177 (65.8)	24 (8.9)	148	99 (66.9)	16 (10.8)	121	78 (64.5)	8 (6.6)
VACV 500 x 1	266	158 (59.4)	25 (9.4)	174	114 (65.5)	15 (8.6)	92	44 (47.8)	10 (10.9)
VACV ‹ 1	269	111 (41.3)	31 (11.5)	157	70 (44.6)	26 (16.6)	112	41 (36.6)	5 (4.5)
ACV 400 x 2	267	168 (62.9)	22 (8.2)	136	86 (63.2)	13 (9.6)	131	82 (62.6)	9 (6.9)
Placebo	134	18 (13.4)	14 (10.4)	69	10 (14.5)	7 (10.1)	65	8 (12.3)	7 (10.8)

It appears that the recurrence free rates were higher and rates of unknowns were lower in Study 037 at Week 16 for VACV 500 mg qd than they were in Study 026. For Study 026, the treatment effect sizes in the two HSV history subgroups were 51.0% and 35.5% and their difference of 15.5% is nearly statistically significant with p-value 0.073 and 95% confidence interval (-0.014, 0.324). There are no apparent explanations for this difference.

Overall, there is evidence that VACV mg bid is better than VACV 500 mg qd, VACV mg bid is better than VACV 1000 mg qd among patients with 9 or fewer recurrences and VACV 1000 mg qd is better than VACV mg bid among patients with 10 or more recurrences per year, and that VACV 1000 mg qd is better than VACV 500 mg qd in males. In balance it appears that VACV mg bid and 1000 mg qd are comparable with both more efficacious than 500 mg qd. The data presented are inadequate to make statistical conclusions regarding relative efficacy for subgroups formed by gender and HSV history.

5) Comparison to Acyclovir

Acyclovir has been approved for suppression of recurrent genital herpes, therefore information on the relative performance of the new treatments over the existing treatment is important. The table below gives 98.75% confidence intervals for VACV containing doses vs. ACV 400 mg bid, which could be interpreted as simultaneous 95% confidence intervals taking multiple comparisons into consideration.

Confidence intervals for the differences of crude proportions
when compared to ACV 400 mg bid
All unknowns are classified as failures
Six Months

Treatment	Overall		HSV Rec. ≤ 9		HSV Rec. > 9	
	98.75% CI	p-value	98.75% CI	p-value	98.75% CI	p-value
VACV . mg bid	-0.110, 0.104	0.9474	-0.080, 0.212	0.2608	-0.235, 0.073	0.1902
VACV 1000 mg qd	-0.097, 0.118	0.8007	-0.146, 0.148	0.9811	-0.140, 0.175	0.7814
VACV 500 mg qd	-0.185, 0.031	0.0749	-0.191, 0.093	0.3900	-0.319, -0.013	0.0214
VACV 250 mg qd	-0.380, -0.178	<0.0001	-0.425, -0.147	<0.0001	-0.427, -0.132	<0.0001

Twelve Months

Treatment	Overall		HSV Rec. ≤ 9		HSV Rec. > 9	
	98.75% CI	p-value	98.75% CI	p-value	98.75% CI	p-value
VACV mg bid	-0.104, 0.101	0.9706	-0.074, 0.216	0.2195	-0.223, 0.059	0.1478
VACV 1000 mg qd	-0.105, 0.100	0.9502	-0.129, 0.154	0.8253	-0.170, 0.127	0.7211
VACV 500 mg qd	-0.163, 0.038	0.1183	-0.170, 0.099	0.5123	-0.266, 0.035	0.0560
VACV mg qd	-0.286, -0.105	<0.0001	-0.312, -0.061	0.0002	-0.341, -0.078	<0.0001

This shows strong evidence that VACV mg qd is inferior to ACV 400 mg bid. It also shows evidence that VACV 500 mg qd may be inferior to ACV 400 mg bid in patients with 10 or more recurrences (interaction p-value = 0.0560). It appears that VACV mg bid is better in patients with 9 or fewer recurrences per year than ACV 400 mg bid while the reverse is true in patients with > 10 recurrences per year. A test of interaction between HSV recurrent history and the comparison of VACV mg bid and ACV 400 mg bid provided support (p = 0.0847) that the relative performance varies by HSV subgroup. Other interactions are summarized in the following table:

Interaction between treatment and HSV recurrent history
All unknowns are treated as failures

Treatments Compared	Crude proportions at 6 months		Crude proportions at 12 months	
	95% CI for the diff. of rel. eff.	Two-sided P-value	95% CI for the diff. of rel. eff.	Two-sided P-value
VACV mg bid vs. ACV 400 mg bid	(-0.020, 0.313)	0.085	(-0.006, 0.312)	0.059
VACV 1000 mg qd vs. ACV 400 mg bid	(-0.185, 0.153)	0.852	(-0.127, 0.195)	0.681
VACV 500 mg qd vs. ACV 400 mg bid	(-0.068, 0.275)	0.235	(-0.078, 0.238)	0.322

The VACV 1000 mg qd is quite similar to ACV 400 mg bid in recurrence free rates in each of the HSV history subgroups. It has not been shown that the relative performance of VACV 500 mg qd and ACV 400 mg bid change with the HSV subgroup (p-value = 0.235 and 0.322 at 6 month and 12 month, respectively).

E: Overall Statistical Reviewer's Assessment

The evaluation of subgroup effects is difficult due to the number of comparisons being made. Never the less the results of the Study 026 and 037 support the following conclusions for the crude proportions of patients recurrence free at the end of six months and twelve months.

I. VACV mg bid, 1000 mg qd, 500 mg qd and mg qd are associated with an increase in the percent of the patients recurrence free in six and twelve months, relative to placebo.

II. VACV mg qd is inferior to VACV mg bid, 1000 mg qd, 500 mg qd and ACV 400 mg bid.

III. VACV mg bid is likely to provide better suppression than VACV 500 mg qd.

IV. VACV mg bid is likely to be relatively more potent among patients with ≤ 9 recurrences than it is among patients with >9 recurrences/year when compared to VACV 1000 mg qd and ACV 400 mg bid.

V. It has not been shown that the relative treatment effects for VACV 1000 mg qd and 500 mg qd differ for patients with ≤ 9 HSV recurrences/year and patients with more than 9 recurrences/year.

VI. Males have higher recurrence free rates than females for all the active arms studied in Study 026. The rates for males and females are comparable in the placebo group.

VII. The proportion of subjects with missing recurrence status, especially at 12 months, makes it difficult to precisely estimate the recurrence free rates, but the conclusions regarding comparative efficacy for VACV mg bid, 1000 mg qd and 500 mg qd are consistent over the various approaches used to incorporate those subjects with incomplete data.

Greg Soon, Ph.D.
Mathematical Statistician

Concur:Paul Flyer, Ph.D. 9/29/97

cc:
Archival IND NDA 20550 SE1-003
HFD-530
HFD-104/Ms. Sage (via TeamLinks)
HFD-530/Dr. Birnkrant (via TeamLinks)
HFD-530/Dr. Behrman
HFD-530/Dr. Cvetkovich
HFD-530/Ms. Truffa
HFD-725/Dr. Flyer
HFD-725/Dr. Soon
HFD-725/Dr. Anello
HFD-725/Ms. Shores

APPEARS THIS WAY
ON ORIGINAL

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This review contains 21 pages.

APPEARS THIS WAY
ON ORIGINAL

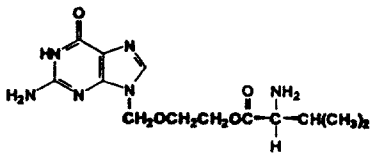
PHARMACOLOGIST'S REVIEW

NDA #: 20-550 (S-003)

DATE SUBMITTED: Nov. 18, 1996
DATE ASSIGNED: Jan. 8, 1997
DATE REVIEW COMPLETED: March 26, 1997
HFD-530

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

DRUG: Valacyclovir hydrochloride (Valtrex®)
CAS REGISTRY #: 124832-27-5
CHEMICAL STRUCTURE:



RELATED DOCUMENTS: IND NDA 18-828 NDA 20-487

INDICATION: Suppressive therapy for genital herpes simplex virus infections

EVALUATION AND CONCLUSION

This submission is a supplemental application to provide for the use of valacyclovir for chronic suppressive therapy of recurrent genital herpes. The sponsor has previously submitted nonclinical pharmacokinetic, pharmacology, and toxicology data sufficient to support this indication and no regulatory action is needed.

Kenneth L. Hastings, Dr.P.H.

concurrences:
HFD-530/ADDir/GChikami 4/14/97
HFD-530/TL/JFarrelly 3/31/97
KENNETH L. HASTINGS/Pharm/3-26-97

disk:
HFD-530/JFarrelly

cc:
HFD-530 (S-003)
HFD-530 Division File
HFD-340
HFD-530/CSO/DStaten
HFD-530/Pharm/KHastings
HFD-530/MO/TCvetkovich
HFD-530/Chem/KLo
HFD-530/Micro/NBiswal

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20550/S-003

MICROBIOLOGY REVIEW(S)

Comments will be included in AP letter 4/7/97

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA 20-550

REVIEWER : N. Biswal
CORRESPONDENCE DATE : 11/18/96
CDER RECEIPT DATE : 11/19/96
REVIEW ASSIGNMENT : 1/08/97
REVIEW COMPLETE DATE : 3/27/97

SPONSOR: GlaxoWellcome Co.
3030 Cornwallis Rd
Research Triangle Park, NC 27709

SUBMISSION REVIEWED: SEI-003

DRUG CATEGORY: Antiviral

INDICATION: Suppressive Therapy for Genital Herpes Simplex Virus Infections

DOSAGE FORM: 500 and 1000 mg Caplets

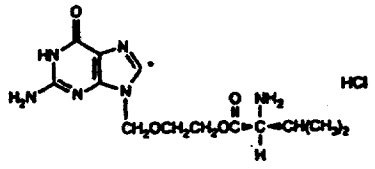
PRODUCT NAMES:

a. **PROPRIETARY:** Valtrex, 256U87

b. **NONPROPRIETARY:** Valacyclovir hydrochloride

c. **CHEMICAL:** L-Valine 2-[(2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy] ethyl ester hydrochloride

STRUCTURAL FORMULA:



Empirical Formula: $C_{13}H_{20}N_6O_4$

Mol. Wt.: 324.34

SUPPORTING DOCUMENTS:
NDA18-828

INTRODUCTION: Genital herpes infections are among the most common sexually transmitted diseases today. Antibody prevalence to herpes simplex viruses varies significantly according to sexual activity, socioeconomic status and race; among sexually active young adults the prevalence may be as high as 50% in the USA. Symptomatic episodes of genital herpes may be classified as initial or recurrent. Initial or primary episodes are quite often acquired during sexual contact with an infected partner and may be associated with clinical manifestation that may range from lack of symptoms to severe symptoms including fever, dysurea, localized inguinal adenopathy, and malaise. Nonprimary first episodes are usually less severe and systemic manifestations are less common.

Like other herpesviruses, both types of HSV are capable of establishing latent infections with subsequent recurrences. It is not clear how the virus escapes from its latent state to initiate a variety of complex pathogenic processes in different organs ranging from simple fever blister to fatal encephalitis. However, recurrent genital infection is the largest reservoir of HSV-2 and invariably is associated with a shorter duration of viral shedding and fewer lesions. Many recurrences are mild, subclinical and HSV may be shed without recognizable lesions or symptoms.

FDA has recently approved Valacyclovir hydrochloride (VACV, Valtrex®) caplets to be administered orally at a dose of 500 mg, twice a day for 5 days, for the treatment of recurrent genital herpes (NDA 20-550). In this supplemental NDA submission the sponsor is seeking approval of Valtrex caplets for the **suppression of recurrent genital herpes.**

VACV is the hydrochloride salt of the L-valyl ester of the acyclic nucleoside analog, acyclovir (ACV). Without any intrinsic antiviral activity, VACV must undergo hydrolysis to ACV, which in turn is selectively phosphorylated in virus infected cells to a triphosphate form to inhibit DNA replication of a number of herpesviruses including herpes simplex virus types 1 (HSV-1) and 2 (HSV-2), and varicella zoster virus (VZV). Sensitivity test results, expressed as the concentration of ACV required to inhibit by 50 % the replication of virus in cell culture (ED_{50}) vary greatly depending upon the particular assay used, the cell type employed, the virus strain and the laboratory performing the test. In general, ACV has demonstrated greater potency against HSV-1 (ED_{50} = 0.02- 13.5 µg/ml) than HSV-2 (ED_{50} = 0.01-9.9 µg/ml) and VZV (ED_{50} = 0.17-10.8 µg/ml). Pharmacokinetic studies have established that the plasma concentrations of ACV achieved with the oral administration of VACV at 500 mg (C_{max} = 3.60 µg/ml) or 1000 mg (C_{max} = 5.55 µg/ml) twice daily was within the ED_{50} range of most HSV strains.

For detailed information on the preclinical virology of VACV, the sponsor has cross referenced to the microbiology section of the first NDA submitted, NDA 20-487, for herpes zoster indication . In addition, preclinical information on the antiviral activities of VACV specifically against HSV infections has been reviewed for the original NDA 20-550. Therefore, new information on the clinical virology of VACV, as it specifically relates to suppression of recurrent genital herpes infection, is reviewed below.

The sponsor has submitted data from two placebo-controlled trials that demonstrate the efficacy and safety of VACV for the suppression of recurrent genital herpes in about 1800 immunocompetent patients. **Study 123-037** was designed to compare the safety and efficacy of VACV 500 mg once daily with placebo for 4 months in patients with HSV recurrence rates of greater than 8 episodes per year. **Study 123-026** was designed to

evaluate three VACV once daily doses (1000 mg, 500 mg, mg), VACV twice daily doses mg) , ACV twice daily (400 mg), and placebo for 12 months in patients with HSV recurrence rates of at least 6 episodes per year. In both the studies, the primary efficacy endpoint was time-to-first recurrence. No virologic parameters were included or evaluated in either of the clinical studies.

THE PACKAGE INSERT

The microbiology section of the package insert for the Valtrex caplets is the same as has been approved for NDA 20-550.

CONCLUSIONS: 1. In this supplemental NDA the sponsor is seeking approval of caplet formulations (500 mg or 1 g) of a prodrug VACV for the suppression of recurrent genital herpes infection in immunocompetent patients. This prodrug is known to be converted to ACV and the plasma concentrations of ACV may reach 3-5 times higher than the levels achieved after oral administration of ACV.

2. VACV caplets have been approved for the treatment of herpes zoster (NDA 20-487), and genital herpes (NDA 20-550) infections. The microbiology section of the current supplement is cross-referenced to the two NDAs submitted and reviewed earlier.

3. The microbiology section of the package insert for VALTREX is the same as has been approved for NDA 20-550.

RECOMMENDATIONS: 1. This NDA supplement is approved with respect to microbiology.

2. As was noted for the original NDA 20-550 , HSV resistance to VACV (ACV) remains a major microbiologic concern especially since ACV-resistant TK mutants with varying degrees of attenuated pathogenicity have been discovered from various patient populations. Please consider designing new, improved and standardized experimental protocols to determine the prevalence and incidence of VACV-resistant mutants of HSV during the phase IV clinical trials.

N. Biswal

Nilambar Biswal, Ph.D.

CONCURRENCES:

HFD-530/Dep Dir Signature 4/3/97 Date

HFD-530/SMicro Signature 4/3/97 Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20550/S-003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-550 SE1-003 **REVIEWER:** B. Davit, Ph.D.
DRUG: VALTREX® (valacyclovir) **FORMULATION:** oral caplets
SUBMISSION DATE: 11/18/96 **APPLICANT:** GlaxoWellcome
LOGGED IN: 6/19/97 **REVIEW FINAL:** 7/25/97

INTRODUCTION: VALTREX® (valacyclovir) is indicated for the treatment of herpes zoster (shingles) and for the treatment of the initial episode and recurrent genital herpes. Approved regimens are: 1000 mg q8h for 7 days for treatment of herpes zoster, 1000 mg q12h for 10 days for treatment of initial episode genital herpes, and 500 mg q12h for treatment of recurrent episodes of genital herpes. According to the label, to date, efficacy has not been established in immunocompromised patients. NDA 20-550 efficacy supplement SE1-003 requests approval for an additional indication; for chronic suppressive therapy of recurrent episodes of genital herpes in immunocompetent patients). The proposed regimen for this new indication is 500 mg q24h for up to one year followed by re-evaluation. Data from two clinical studies, 123-026 and 123-037, were submitted in support of this efficacy supplement. The submitted draft revised package insert proposes to add, to the CLINICAL PHARMACOLOGY (Drug Interactions) section of the label, a summary of findings from recently completed drug-drug interaction studies of valacyclovir-digoxin and valacyclovir-antacids (aluminum hydroxide and magnesium hydroxide). This submission also contains two pharmacokinetic reports in which acyclovir exposure was estimated following sparse sampling of patients in studies 123-026 and 123-037, and a pharmacokinetic report in which acyclovir exposure at various VALTREX® and ZOVIRAX® dosing regimens was estimated based on a literature review and data from the company's prior pharmacokinetic studies of valacyclovir.

SUMMARY: No interactions in acyclovir pharmacokinetics were observed following single-dose administration of 1000 mg valacyclovir with antacids or digoxin. Digoxin pharmacokinetics (following the second of two 0.75 mg doses given 12 hr apart) were not affected by multiple-dose administration of valacyclovir 1000 mg q8h. Plasma acyclovir exposure was estimated in the pivotal Phase III Study 123-026, in which various acyclovir and valacyclovir regimens were administered for 52 weeks to compare suppression of recurrent episodes of genital herpes. Recurrences were fewest in groups receiving acyclovir 400 mg q12h (the approved ZOVIRAX® regimen for this indication), valacyclovir mg q12h, and valacyclovir 1000 mg q24h. Review of the acyclovir exposure estimate data suggested that, in the these three groups, plasma acyclovir concentrations exceeded some threshold level (such as IC_{50}) for the longest time duration.

BACKGROUND: See the ClinPharm/Biopharm Review of NDA 20-487 (6/95) for a detailed description of the clinical pharmacokinetics of valacyclovir and acyclovir following valacyclovir administration.

Valacyclovir is rapidly and extensively converted to acyclovir by pre-systemic metabolism after oral administration. In escalating single-dose (up to 1000 mg) and multiple-dose (up to 2000 mg q24h) studies, less than dose-proportional increases

of acyclovir AUC and Cmax were observed with increasing valacyclovir doses. The acyclovir Tmax also displayed dose-dependency with greater values as valacyclovir doses increased, suggesting saturation of absorption sites along the GI tract. Elimination half-life of acyclovir after valacyclovir administration was 2.5 to 3 hr and there was no evidence, from the multiple-dose studies, that repeated administration of valacyclovir for 11 days resulted in any appreciable change in acyclovir concentrations over time.

Plasma concentrations of valacyclovir are typically below assay LLOQ (0.25 μM) within three hr of administration. Thus, valacyclovir pharmacokinetic parameters other than peak concentration are not estimable. The molar ratio of peak concentration of valacyclovir to acyclovir averaged 4% at the different valacyclovir dose levels, suggesting that the conversion of valacyclovir to acyclovir was not saturated at the valacyclovir doses studied.

Valacyclovir is converted to acyclovir and L-valine by a mitochondrial hydrolase which has been isolated in rat small intestine, lung, and liver. In humans, its activity predominates in liver. Acyclovir is partially metabolized to 9-carboxymethoxymethylguanine (CMMG) in the liver by cytosolic enzymes. CMMG is not detected in plasma except in some subjects with severe renal impairment.

Less than 1% of a valacyclovir dose is recovered unchanged in the urine within 24 hr. Forty to fifty percent of the dose is recovered as acyclovir representing 80-85% of the total urinary recovery of drug-related material. Urine recovery of CMMG ranged from 7-12% of the dose. The pharmacokinetic profile of acyclovir after oral administration of 1000 mg valacyclovir was not appreciably modified in elderly, subjects with advanced HIV disease, or subjects with impaired hepatic function. No clinically significant drug interactions were observed with thiazide diuretics, cimetidine, or probenecid administered at therapeutic doses.

VALTREX® is available as 500 and 1000 mg caplets.

SYNOPSIS OF SUBMISSION SE1-003:

A randomized four-way crossover study in 12 healthy subjects was conducted to investigate the potential for a drug-drug interaction between valacyclovir and digoxin in healthy volunteers. Effects of digoxin were assessed by comparing acyclovir pharmacokinetics following a single 1000 mg valacyclovir dose versus a single 1000 mg valacyclovir dose administered concomitantly with the second of two 0.75 mg doses of digoxin, given 12 hr apart. Acyclovir pharmacokinetics were comparable in the two groups:

Acyclovir pharmacokinetic parameters in 12 healthy normal subjects
1000 mg valacyclovir single dose given alone or in combination with two 0.75 mg digoxin doses given 12 hr apart
N=12 except where indicated

Treatment	C_{max} (ng/mL)	med T_{max} (hr)	AUC_∞ (ng·hr/mL)	$T_{1/2}$ (hr)	CL/F (mL/min)	CL_R (mL/min)	F_e (%)	V/F (L)
valacyclovir	4.98±1.29	2.5	19.7±4.5	2.27±0.16	625±145	279±72	42.6±9.8	123±33
combination	5.14±1.23	2.0	20.1±4.2	2.24±0.15	611±156	278±49	43.5±8.0	119±33

To determine the effects of valacyclovir on digoxin pharmacokinetics, the pharmacokinetics of digoxin following the second of two 0.75 mg doses given 12 hr apart were compared with those determined when valacyclovir was administered at 1000 mg q8h for 8 days, initiated 12 hr before the first of two 0.75 mg digoxin doses given 12 hr apart. Digoxin pharmacokinetics were comparable in the two groups:

Dixgoxin pharmacokinetic parameters in 12 healthy normal subjects Two 0.75 mg digoxin doses given 12 hr apart alone or in combination with valacyclovir 1000 mg q8h for 8 days							
Treatment	C_{max} (ng/mL)	median T_{max} (hr)	AUC_∞ (ng·hr/mL)	$T_{1/2}$ (hr)	CL/F (mL/min)	CL_R (mL/min)	V/F (L)
digoxin	3.45±0.95	1.0	42.6±11.5	37.8±7.4	318±79	73.8±27.5	1045±354
combination	3.32±0.88	1.0	40.6±15.2	40.1±7.2	367±169	81.0±31.3	1260±576

The effects of co-administration of antacids and valacyclovir on acyclovir bioavailability were determined in a randomized crossover study in 18 healthy normal subjects. The pharmacokinetics of acyclovir were compared following administration of a single 1000 mg dose of valacyclovir, 30 mL MAALOX given 30 minutes prior to a single 1000 mg valacyclovir dose, and 30 mL MAALOX given 65 minutes following a single 1000 mg valacyclovir dose. Valacyclovir pharmacokinetics were comparable in the three groups:

Acyclovir pharmacokinetic parameters (N=18) Treatment A: 30 mL MAALOX® given 30 minutes before a single 1000 mg dose of VALTREX® Treatment B: 30 mL MAALOX® given 65 minutes after a single 1000 mg dose of VALTREX® Treatment C: VALTREX 1000 mg single dose given alone					
Treatment	C_{max} (µg/mL)	median T_{max} (hr)	AUC_∞ (µ·hr/mL)	$T_{1/2}$ (hr)	CL/F (mL/min)
A	4.89±0.94	1.25	21.7±4.2	2.73±0.28	674±125
B	4.67±1.21	1.5	17.7±3.5	2.7±0.28	667±118
C	4.57±1.14	1.5	18.2±2.9	2.67±0.22	643±102

Findings from two pivotal trials were submitted in support of this efficacy supplement. Study 123-037 was a placebo-controlled trial of valacyclovir for the suppression of recurrent genital herpes in immunocompetent patients. Patients received either VALTREX 500 mg or placebo once daily for 16 weeks, followed by an open-label phase in which all patients took VALTREX® 500 mg q24h until they had participated in the study for a total of 48 weeks. VALTREX® was significantly better than placebo in this study. Study 123-026 was a comparative trial of 4 dosage regimens of valacyclovir with acyclovir and placebo in the same patient population. Regimens were VALTREX® mg q12h, 1000 mg q24h, 500 mg q24h, mg q24h, ZOVIRAX® 400 mg q12h, and placebo. All of the VALTREX® and ZOVIRAX® regimens were significantly better than placebo in preventing or delaying recurrences of genital herpes during the one year study period. However, in patients with more than 9 HSV recurrences per year, recurrences were lowest in the groups receiving mg q12h and 1000 mg q24h. In patients with fewer than 9 HSV recurrences per year, the regimens of mg q12h, 500 mg q24h, and 1000 mg q24h were equally effective. A clear dose-response relationship was seen across the three once-daily valacyclovir dosing regimens. Valacyclovir 500 mg once daily provided adequate clinical efficacy for most patients, but those with a history

of more than 9 recurrences a year appeared to require an alternative dose of 1000 mg once daily or mg twice daily.

Plasma samples were collected from patients in Study 123-026 to monitor acyclovir concentrations. These concentration-time data were used to estimate acyclovir exposure from each of the valacyclovir and acyclovir dosing regimens. The acyclovir pharmacokinetic estimates from Study 123-026 were consistent with data from Phase I studies of acyclovir and valacyclovir in healthy adults:

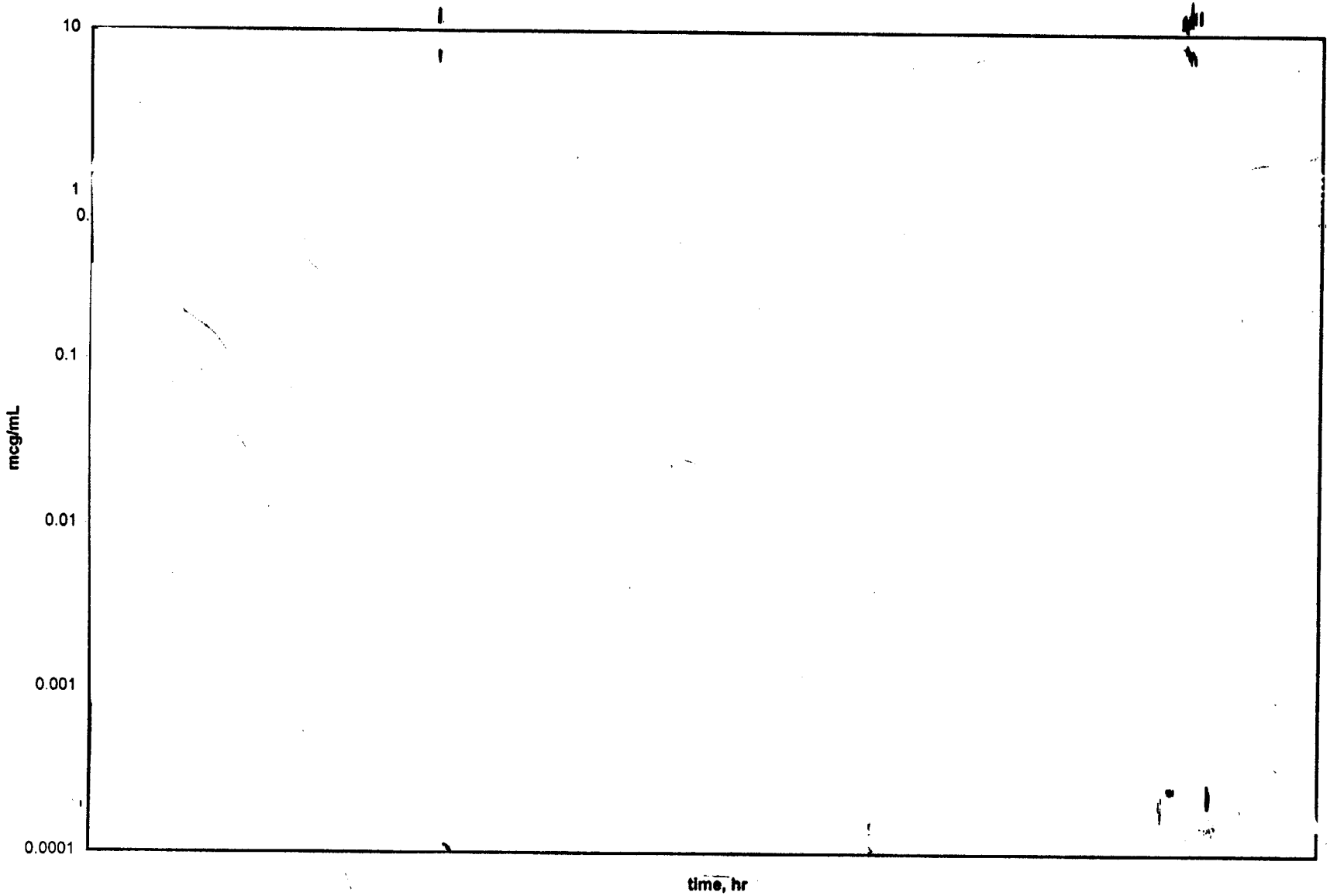
Drug Regimen	Daily AUC (μg*hr/mL)	C_{max} (μg/mL)	C_{min} (μg/mL)
Valacyclovir mg q12h	12.39	1.57	0.10
Valacyclovir 1000 mg q24h	18.13	5.13	0.04
Valacyclovir 500 mg q24h	10.35	2.48	0.02
Valacyclovir mg q24h	4.95	1.36	0.01
Acyclovir 400 mg q12h	7.60	0.67	0.10

For the once-daily regimens, the increasing peak concentrations and AUCs of acyclovir associated with increasing valacyclovir doses were consistent with the efficacy dose-response profile. However, the comparable efficacy results observed between the valacyclovir 1000 mg once-daily, valacyclovir mg twice-daily and acyclovir 400 mg twice daily regimens could not be explained on the basis of plasma acyclovir Cmax nor daily AUC values alone. As shown in the attached figure (page 5) comparing simulated acyclovir concentration-time profiles, acyclovir plasma concentrations following either a valacyclovir mg q12h or 1000 mg q24 hr regimen would exceed a minimum threshold (such as *in vitro* IC_{50} or trough concentrations from the acyclovir twice-daily regimen) for a longer time duration each day than concentrations following a valacyclovir 500 mg q24h regimen. It may be efficacy is best associated with time above a threshold or acyclovir Cmin relative to a threshold.

LABEL: The draft package insert proposes the following: (1) inclusion of summaries of findings from the drug-drug interaction studies of valacyclovir-digoxin and valacyclovir-antacids; (2) modification of Table 3 (Dosages for Patients with Renal Impairment) to include recommendations for renally-impaired patients who receive VALTREX® for suppressive therapy.

RECOMMENDATIONS: The recommendation by DAVDP that the appropriate regimens for the suppression of genital herpes are mg q12h or 1000 mg q24h is supported by acyclovir plasma concentration data from Study 123-026. DPEIII recommends that the VALTREX® package insert be modified to briefly summarize the results of the drug-drug interactions studies of valacyclovir and digoxin and valacyclovir and antacids. DPEIII also recommends use of the following regimens for suppressive therapy of immunocompetent patients: 1000 mg q24h for patients with creatinine clearance greater than or equal to 30 mL/min, and 500 mg q24h for patients with creatinine clearance lower than 29 mL/min. These regimens are consistent with the present recommended dose adjustments, which were determined based upon review of the applicant's previously conducted pharmacokinetic study of valacyclovir pharmacokinetic in renal impairment (See ClinPharm/Biopharm Reviews of NDAs 20-487 and 20-550).

Simulated plasma acyclovir concentration vs time, various VALTREX dosing regimens



Simulation using WINNONLIN

Data from Study 123-023

PK parameters determined using WINNONLIN

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cc: HFD-530 NDA 20-550
/MO/TCvetkovich
/CSO/DStaten
HFD-340 /Viswanathan
HFD-880 /DPEIII/BDavit
/DPEIII/JJenkins

✓ HFD-880 /DPEIII/DivFiles

✓ /CDR/BMurphy

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REVIEW

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The draft package insert and Appendix I are on file in the Division of Pharmaceutical Evaluation III.

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I. EFFECT OF DIGOXIN ON VALACYCLOVIR PHARMACOKINETICS

Study No. 123-034: REPORT OF THE PHARMACOKINETICS OF ACYCLOVIR AND DIGOXIN FOLLOWING ADMINISTRATION OF DIGOXIN AND VALACYCLOVIR ALONE AND IN COMBINATION IN HEALTHY VOLUNTEERS (NDA 20-550 SE1-003, Vol. 8.2, pp 33-539, Vol. 8.3, pp 1-102).

Objective: To determine: (1) the effects of valacyclovir administration on digoxin pharmacokinetics; and (2) to determine the effects of digoxin on acyclovir pharmacokinetics following valacyclovir administration.

Background: Digoxin is indicated for the treatment of heart failure, and for the control of atrial fibrillation and flutter. About 70% of an oral dose of digoxin is absorbed, and peak plasma concentrations occur from 0.75 to 2 hr following dosing. Binding to plasma proteins is low, about 25%. The volume of distribution is high, about 7 L/kg in patients with normal renal function. The elimination half-life averages 36 hr. About 80% of a dose is excreted in the urine as parent drug. Like valacyclovir, digoxin is thought to be eliminated by active tubular secretion in the kidney. Digoxin is not removed effectively by peritoneal or hemodialysis due to the large volume of distribution. Approximately 10% of the population harbors the enteric bacterium *Eubacterium lentum*, which can convert digoxin into inactive metabolites. The most common digoxin-associated adverse events include cardiac arrhythmia's (ventricular premature contractions, ventricular tachycardia, AV dissociation) and gastrointestinal disturbances. LANOXIN® is available as 0.125, 0.250, 0.375, and 0.500 mg scored tablets.

The therapeutic index of digoxin is narrow. Plasma concentrations of at least 0.8 ng/mL must be achieved for digoxin to exert an inotropic effect, but digoxin-induced arrhythmia's can occur at plasma concentrations as low as 2.0 ng/mL. Digoxin therapy is generally initiated with loading doses to achieve the desired plasma concentrations; thereafter maintenance doses are given q24h. Steady-state plasma digoxin concentrations are generally achieved from 6-10 days after initiation of dosing. Age, renal function, lean body mass, and possible drug-drug interactions must be considered in determining the optimal dose. The package insert gives a dosing nomogram based on lean body weight and renal function (estimated by CL_{CR} in mL/min/70 kg) and provides an example that a 70 kg patient with normal renal function would generally require 0.75 to 1.25 mg q24h as a maintenance dose. However, the package insert also cautions that the recommended doses are average values, and states that measuring plasma digoxin concentrations can be helpful in optimizing the dose. Digoxin therapeutic drug monitoring (TDM) is recommended in clinical practice.

The package insert lists many drugs which are known to change or thought to potentially alter digoxin blood concentrations when co-administered. Due to the considerable variability of these interactions, it is recommended that digoxin dosage be carefully individualized when patients receive co-administered medications. The package insert also states that caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function.

Study Rationale: Digoxin is commonly prescribed in the elderly, which is a major target population for treatment of herpes zoster. Both acyclovir and digoxin are eliminated

primarily as unchanged drug in the urine, and both drugs are thought to be excreted by glomerular filtration with tubular secretion as an important component of renal elimination. Thus, there is the potential for an interaction between digoxin and acyclovir.

Investigators: J Soul-Lawton, PhD (Principle Investigator) and RW Peck, MD (Study Physician), Wellcome Clinical Investigation Unit, London, UK.

Subjects: A total of 12 healthy, male (5) and female (7) volunteers enrolled in and completed the study. Mean demographic parameters were: age 31 years (range 22-44 years) , body wt 75 kg (range 51-99 kg). Individual demographic data are listed in Appendix I, Table 1.

Formulation: Valacyclovir as marketed 500 mg VALTREX® tablets, Batch No. 93L5112. Digoxin as marketed 0.375 mg LANOXIN® tablets, V0552A. Both drugs were provided by GlaxoWellcome.

Study Design: This was an open-label, randomized, balanced, 4-way crossover study. On each occasion, after an overnight fast, subjects received one of the following:

- Single dose valacyclovir, 1000 mg (PK sampling initiated at the time of the single valacyclovir dose);
- Two 0.75 mg digoxin doses separated by 12 hr (PK sampling initiated at the time of the second digoxin dose);
- Two 0.75 mg digoxin doses separated by 12 hr and 1000 mg valacyclovir q8h for 8 days, started 12 hr before the first dose of digoxin (PK sampling initiated at the time of the second digoxin dose);
- Two 0.75 mg digoxin doses separated by 12 hr, and a single dose of valacyclovir 1000 mg given with the second dose of digoxin (PK sampling initiated at the time of the second digoxin dose).

Pharmacokinetic sampling was initiated on Study Day 1, at the time of the second digoxin dose for all digoxin groups and at the time of the single valacyclovir dose for the valacyclovir-only group. Subjects were fasted from midnight until 2-hr post-dosing for pharmacokinetic sampling. The morning doses of valacyclovir and digoxin were administered concomitantly in those subjects receiving the combination. Subjects were confined during the first two dosing days. After the 24 hr blood and urine samples were taken, subjects were released, and returned to the unit for collection of additional blood samples through Study Day 8. In the digoxin + multi-dose valacyclovir group, subjects self-administered valacyclovir after release from the unit.

For all subjects receiving digoxin, the washout period between treatments was at least 2 weeks. For the subjects receiving valacyclovir only, the washout period was 2 days between the valacyclovir-only treatment and the next treatment.

The dosing schedule is attached.

Sampling: Relative to the morning dose on pharmacokinetic sampling days, blood samples were taken at the following times: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8,

12, 24, 32, 48, 72, 96, and 168 hr. Pharmacokinetic blood samples were not collected after 12 hr post-dosing in the valacyclovir-only group. Urine samples were taken from 0-12 and 12-24 hr post-dosing on pharmacokinetic sampling days.

Analytical methodology:

[redacted]

Pharmacokinetic evaluation: Noncompartmental analysis was used to determine pharmacokinetic parameter estimates. For digoxin, C_{max} and AUC_{∞} were measured after the second dose of digoxin and corrected for pre-dose concentration as follows:

$$C_{max(corrected)} = C_{max(observed)} - C_0 * e^{-\lambda * T_{max}}$$
$$AUC_{\infty(corrected)} = AUC_{\infty} - C_0/\lambda$$

Where C_0 was the pre-dose concentration for the second dose. This was done because the digoxin plasma profile after the second dose was not at steady-state (with the digoxin half-life of approximately 40 hr). The AUC_{∞} and C_{max} obtained after correction would approximate those following a single dose, and allow calculation of CL/F and V/F.

Statistical evaluation: The effect of co-administration of valacyclovir on digoxin pharmacokinetics was investigated by comparing the digoxin alone data with the digoxin + multiple-dose valacyclovir data. The effect of co-administration of digoxin on acyclovir pharmacokinetics was investigated by comparing the single dose valacyclovir data with the single-dose valacyclovir + digoxin data. Except for T_{max}, all parameters were log-transformed before analysis and ANOVA was used to estimate the difference between treatments and 95% confidence intervals. Sources of variation in the ANOVA model were subject, period, and treatment. Differences between T_{max} medians were estimated with 95% confidence intervals using a method based on the Wilcoxon signed rank test.

Safety: Blood samples for clinical laboratory determinations were taken at baseline and on Study Day 7 at the end of each treatment (this was the last day of valacyclovir dosing for the multi-dose valacyclovir group). ECG monitoring took place from the time of the first digoxin dose until 24 hr after the second digoxin dose (a total of 36 hr). Adverse events were monitored throughout the study.

No adverse events occurred during the valacyclovir-only treatment. With one exception, mild or moderate nausea was the major adverse event noted in subjects receiving digoxin, either alone or with valacyclovir. One female subject (No. 9) had nausea and vomiting after the second digoxin dose during her first digoxin treatment (digoxin alone). Her digoxin dose was reduced from 0.75 mg to 0.5 mg for the remaining two digoxin treatments (both of which included valacyclovir). For analysis of pharmacokinetic data

from this subject, plasma and urine digoxin concentration data obtained during the valacyclovir-digoxin treatments were dose-normalized (by multiplying by 1.5).

Results: Mean±S.D. (range) pharmacokinetic parameters of digoxin were:

Digoxin pharmacokinetic parameters Two 0.75 mg digoxin doses given 12 hr apart alone or in combination with valacyclovir 1000 mg q8h for 6 days N=12 except where indicated							
Treatment	C_{max} (ng/mL)	T_{max} § (hr)	AUC∞ (ng·hr/mL)	$T_{1/2}$ (hr)	CL/F (mL/min)	CL_R (mL/min)	V/F (L)
digoxin	3.45±0.95	1.0	42.6±11.5	37.8±7.4 30.1-55	318±79‡ 181-461	73.8±27.5‡ 42-128	1045±354 518-1801
digoxin + valacyclovir	3.32±0.88	1.0	40.6±15.2	40.1±7.2 29.6-53.7	367±169‡ 193-751	81.0±31.3‡ 41-128	1260±576 704-2429
§ median value; ‡ N = 11 AUC∞ and C_{max} were corrected for pre-dose concentration							

Mean digoxin pharmacokinetic parameters were comparable whether two 0.75 mg doses, separated by 12 hr, were administered alone or in combination with valacyclovir treatment, which was initiated 12 hr before the first digoxin dose and given at 1000 mg q8h throughout the digoxin blood sampling period (7 days). In general, individual digoxin pharmacokinetic parameter values were also comparable in the two treatment groups.

Point estimates and 95% CIs for the ratio (digoxin + valacyclovir:digoxin alone) for various digoxin pharmacokinetic parameters were:

Digoxin, point estimate and 95% confidence intervals for pharmacokinetic parameters Reference = digoxin; Test = digoxin + valacyclovir			
Parameter	Geometric mean ratio	95% CI	P value
AUC∞	0.91	0.73,1.15	0.390
C_{max}	0.79	0.79,1.17	0.668
$T_{1/2}$	1.06	0.96,1.17	0.198
CL_R	1.10	0.90,1.50	0.596
V/F	1.16	0.89,1.00	0.217

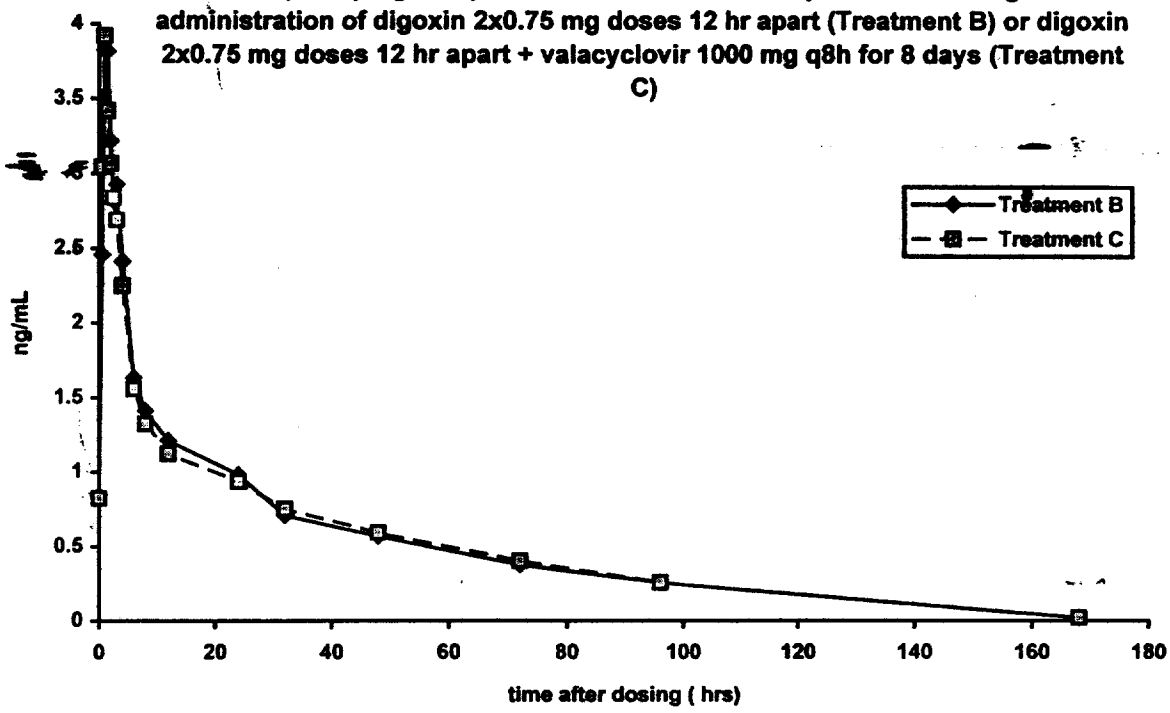
The point estimates and 95% CI for the median difference for T_{max} were:

Digoxin, median difference and 95% confidence interval for T_{max} Reference = digoxin; Test = digoxin + valacyclovir			
Parameter	Median difference	95% CI	P value
T_{max}	-0.25	-0.50,0.25	0.516

Thus, there were no statistically significant differences between the pharmacokinetic parameters of digoxin whether administered alone or in combination with valacyclovir 1000 mg q8h.

The following figure compares the plasma digoxin concentration-time profiles following administration of digoxin alone or in combination with valacyclovir:

Mean (N=12) digoxin plasma concentration-time profiles following oral administration of digoxin 2x0.75 mg doses 12 hr apart (Treatment B) or digoxin 2x0.75 mg doses 12 hr apart + valacyclovir 1000 mg q8h for 8 days (Treatment C)



Mean±S.D. pharmacokinetic parameters of acyclovir were:

Acyclovir pharmacokinetic parameters 1000 mg valacyclovir single dose given alone or in combination with two 0.75 mg digoxin doses given 12 hr apart N=12 except where indicated								
Treatment	C_{max} (ng/mL)	T_{max} § (hr)	AUC_∞ (ng·hr/mL)	$T_{1/2}$ (hr)	CL/F (mL/min)	CL_R (mL/min)	F_e (%)	V/F (L)
valacyclovir	4.98±1.29 3.56-7.42	2.5 1.5-3.0	19.7±4.5 12.8-28.7	2.27±0.16 2.04-2.55	625±145 ‡ 408-915	279±72 ‡ 209-427	42.6±9.8 26.8-63	123±33 74-196
valacyclovir + digoxin	5.14±1.23 3.16-7.68	2.0 1.5-3.0	20.1±4.2 12.4-26.0	2.24±0.15 1.99-2.47	611±156 ‡ 451-947	278±49 ‡ 213-358	43.5±8.0 33.6-58.7	119±33 78-195
§ median value; ‡ N = 10								

Acyclovir pharmacokinetic parameters were comparable whether a single 1000 mg dose of valacyclovir was given alone or in combination with the second of two digoxin 0.75 mg doses given 12 hr apart.

Point estimates and 95% CIs for the ratio (valacyclovir + digoxin:valacyclovir alone) for various acyclovir pharmacokinetic parameters were:

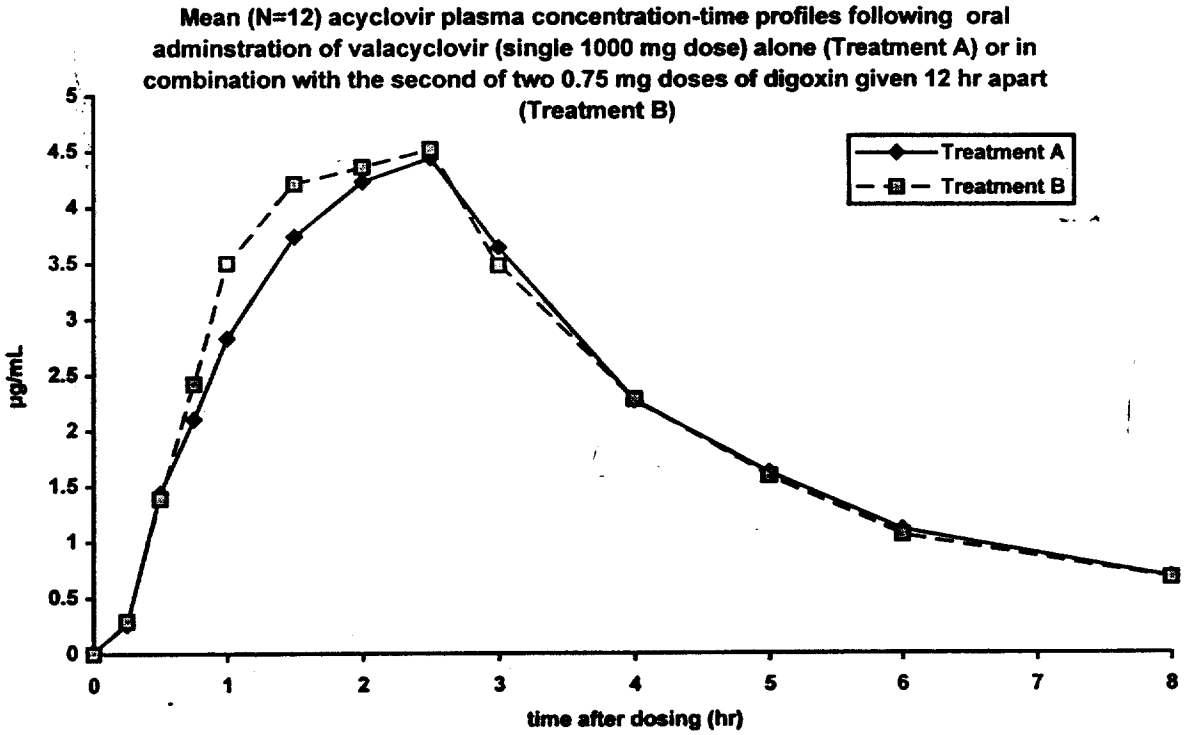
Acyclovir, point estimate and 95% confidence intervals for pharmacokinetic parameters Reference = valacyclovir; Test = valacyclovir + digoxin			
Parameter	Geometric mean ratio	95% CI	P value
AUC_∞	1.03	0.94,1.11	0.507
C_{max}	1.03	0.94,1.13	0.446
$T_{1/2}$	0.99	0.97,1.01	0.328
CL_R	1.01	0.89,1.16	0.827
V/F	0.97	0.88,1.05	0.390

The point estimates and 95% CI for the median difference for T_{max} were:

Acyclovir, median difference and 95% confidence interval for T_{max} Reference = valacyclovir; Test = valacyclovir + digoxin			
Parameter	Median difference	95% CI	P value
T_{max}	-0.25	-0.50,0.23	0.129

There were no statistically significant differences between the pharmacokinetic parameters of digoxin.

The following figure compares the steady-state plasma acyclovir concentration-time profiles following administration of valacyclovir alone or valacyclovir + digoxin:



Discussion: The doses used in this study are clinically relevant. The valacyclovir regimen used in this study is similar to the recommended regimen (1000 mg q8h for 7 days) for the treatment of herpes zoster. However, digoxin pharmacokinetics were studied under non-steady-state conditions, as steady-state plasma digoxin concentrations are generally achieved from 6-10 days after initiation of dosing. It is recommended that the valacyclovir package insert state that there was no interaction between the two, and include a brief description of the study design. The pharmacokinetic parameters of acyclovir following administration of a 1000 mg single dose of valacyclovir were in good agreement with those previously reported (See ClinPharm/Biopharm Review of NDA 20-487). There are few reports of digoxin pharmacokinetic parameters in the current literature; however, the mean $T_{1/2}$ of 38 hr in this study is consistent with $T_{1/2}$ of 40 hr described previously.

Since the target population for valacyclovir and digoxin co-administration will include elderly patients, the known effects of aging on acyclovir and digoxin pharmacokinetics will be briefly discussed here. From information in the valacyclovir package insert, there appeared to be no difference in the acyclovir half-life in elderly subjects (N=9, mean age 74 yr, mean half-life of 3.1 hr) compared with healthy volunteers (N=33, mean age 41 yr, mean half-life of 2.9 hr) following a single 1000 mg dose of valacyclovir. The valacyclovir package insert states that dose adjustment may be necessary in geriatric patients with reduced renal function. Valacyclovir and digoxin dose adjustments are recommended in renal impairment; moreover, the digoxin package insert stresses use of TDM to individualize digoxin therapy. It is important that elderly patients with impaired renal function receive properly adjusted doses of valacyclovir and digoxin when these two are given in combination.

Summary and Conclusion: The objective of this study was to determine if there was the potential for a drug-drug interaction between valacyclovir and digoxin in healthy volunteers. Acyclovir pharmacokinetics were comparable when a single 1000 mg valacyclovir dose was administered either alone or in combination with the second of two 0.75 mg doses of digoxin administered 12 hr apart. Digoxin pharmacokinetics were comparable when two 0.75 mg doses, given 12 hr apart, were administered alone or in combination with valacyclovir 1000 mg q8h for 8 days. Valacyclovir and digoxin were well-tolerated when administered concurrently, based on vital signs, ECG, clinical laboratory and adverse event data. It is recommended that the findings from this study be summarized in the VALTREX® package insert.

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II. EFFECT OF ANTACIDS ON VALACYCLOVIR PHARMACOKINETICS

Study No. 123-038: REPORT OF THE EFFECT OF AN ALUMINUM HYDROXIDE AND MAGNESIUM HYDROXIDE CONTAINING ANTACID ON THE PHARMACOKINETICS OF ACYCLOVIR FOLLOWING A SINGLE ORAL DOSE OF VALACYCLOVIR IN HEALTHY VOLUNTEERS (NDA 20-550 SE1-003, Vol. 8.3, pp. 103-614).

Objective: To determine the effect of an aluminum hydroxide and magnesium hydroxide containing antacid (MAALOX) on the pharmacokinetics of a single 1000 mg oral dose of valacyclovir.

Background/Rationale: A brief synopsis of valacyclovir first-pass metabolism will be provided here. See the ClinPharm/Biopharm Review of NDA 20-487 (6/95) for details.

The absolute bioavailability of acyclovir following oral valacyclovir is about 55%. This suggests significant first-pass intestinal and hepatic metabolism of the prodrug. Valacyclovir is rapidly hydrolyzed to acyclovir *in vitro* in rat liver and intestine.

Administration of antacids could potentially affect the bioavailability of acyclovir from orally-administered valacyclovir, since antacids affect the absorption of many drugs by increasing gastric pH, affecting gastric emptying, or binding to the drug to form insoluble salts. This study was therefore carried out to examine effects on acyclovir pharmacokinetics following administration of a single dose of MAALOX (an aluminum hydroxide and magnesium hydroxide containing antacid) with a single dose of valacyclovir. If an interaction was observed, a proposal would be made to recommend a time interval between administration of valacyclovir and MAALOX.

Investigators:

Subjects: Eighteen male (N=9) and female (N=9) subjects participated. Mean age±S.D. was 24±3 yr, mean height±S.D. was 174±10 cm, and mean±S.D. body weight was 65±9 kg. Individual demographic data are in Table 6, Appendix I.

Formulation: Valacyclovir as the 500 mg marketed tablets (Lot No. 94B5299). The MAALOX (Lot No. 9755) used in this study contained 523.5 mg aluminum hydroxide and 598.5 mg magnesium hydroxide per 15 mL of oral suspension.

Study Design:

- *Treatment A:* 30 mL MAALOX® administered 30 minutes before a single 1000 mg valacyclovir dose
- *Treatment B:* 30 mL MAALOX® administered 65 minutes after a single 1000 mg valacyclovir dose
- *Treatment C:* 1000 mg single valacyclovir dose

A 30 mL MAALOX® dose was selected as the usual dosing regimen is 10-20 mL taken about 90 minutes after meals. It was administered 30 minutes prior to valacyclovir dosing as its rate of antacid powder release is 71 to 92% at 30 minutes post-dose.

Hence, the administration of 30 mL MAALOX® 30 minutes prior to valacyclovir administration (Treatment A) was the situation where any potential interaction is the most likely to bee seen. Valacyclovir is rapidly absorbed with a Tmax of about 1 hr following a 1000 mg oral dose. Hence, MAALOX® was given 65 minutes after valacyclovir administration (Treatment B) when most of the valacyclovir dose was likely to be absorbed.

Subjects fasted from 8 hr prior to until 4 hr after valacyclovir administration.

Sampling: Blood samples were collected immediately prior to dosing and at 0.25, 0.5, 0.75, 1. 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15 and 24 hr after the valacyclovir dose.

Analytical methodology:

The assays were performed at the Dept. of Bioanalysis and Drug Metabolism at the Wellcome Research Laboratories, Beckenham, Kent, UK. Details of the validation of the analytical method are provided in this review (page 25).

Pharmacokinetic evaluation: Noncompartmental analysis. The elimination rate constant (λ) was determined using plasma concentrations measured from 6 to 15 hr after dosing.

Statistical evaluation: ANOVA was performed on ln-transformed pharmacokinetic parameters C_{max}, AUC_{24}, AUC_{∞}, $T_{1/2}$, and CL/F. T_{max} data were analyzed by nonparametric methods (Friedman test). 95% CIs of mean differences between treatment groups and ratio estimates were calculated. For T_{max}, non-parametric 95% CIs were calculated for median differences between treatment groups.

Safety: Two subjects reported mild-to-moderate gastric discomfort. These adverse events were considered possibly related to MAALOX® administration. No adverse events associated with valacyclovir administration were noted.

Results: Acyclovir pharmacokinetic parameters were comparable in the three treatment groups. Mean±S.D. (range) pharmacokinetic parameters of acyclovir were:

Acyclovir pharmacokinetic parameters (N=18)
Treatment A: 30 mL MAALOX® given 30 minutes before a single 1000 mg dose of VALTREX®
Treatment B: 30 mL MAALOX® given 65 minutes after a single 1000 mg dose of VALTREX®
Treatment C: VALTREX 1000 mg single dose given alone

Treatment	C_{max} (µg/mL)	T_{max} § (hr)	AUC_∞ (µ·hr/mL)	$T_{1/2}$ (hr)	CL/F (mL/min)
A	4.89±0.94	1.25	21.7±4.2	2.73±0.28	674±125
B	4.67±1.21	1.5	17.7±3.5	2.7±0.28	667±118
C	4.57±1.14	1.5	18.2±2.9	2.67±0.22	643±102

§ median value

Point estimates and 95% CIs for the ratio for acyclovir PK parameters for MAALOX® given 30 minutes prior to a single 1000 mg dose of valacyclovir were:

Acyclovir, point estimate and 95% confidence intervals for pharmacokinetic parameters
Reference = 1000 mg valacyclovir; Test = 1000 mg valacyclovir + MAALOX 30 minutes before valacyclovir dose

Parameter	Geometric mean ratio	95% CI
AUC_∞	0.96	0.90,1.02
C_{max}	1.08	0.99,1.18
$T_{1/2}$	1.02	0.99,1.05
CL/F	1.04	0.98,1.11

The point estimates and 95% CI for the median difference for T_{max} were:

Acyclovir, median difference and 95% confidence interval for T_{max}
Reference = 1000 mg valacyclovir; Test = 1000 mg valacyclovir + MAALOX 30 minutes before valacyclovir dose

Parameter	Median difference	95% CI
T_{max}	0	-1.0-0.0

Point estimates and 95% CIs for the ratio for acyclovir PK parameters for MAALOX® given 65 minutes following a single 1000 mg dose of valacyclovir were:

Acyclovir, point estimate and 95% confidence intervals for pharmacokinetic parameters
Reference = 1000 mg valacyclovir; Test = 1000 mg valacyclovir + MAALOX 65 minutes after valacyclovir dose

Parameter	Geometric mean ratio	95% CI
AUC_∞	0.97	0.91,1.03
C_{max}	1.02	0.93,1.12
$T_{1/2}$	1.01	0.98,1.04
CL/F	1.03	0.97,1.10

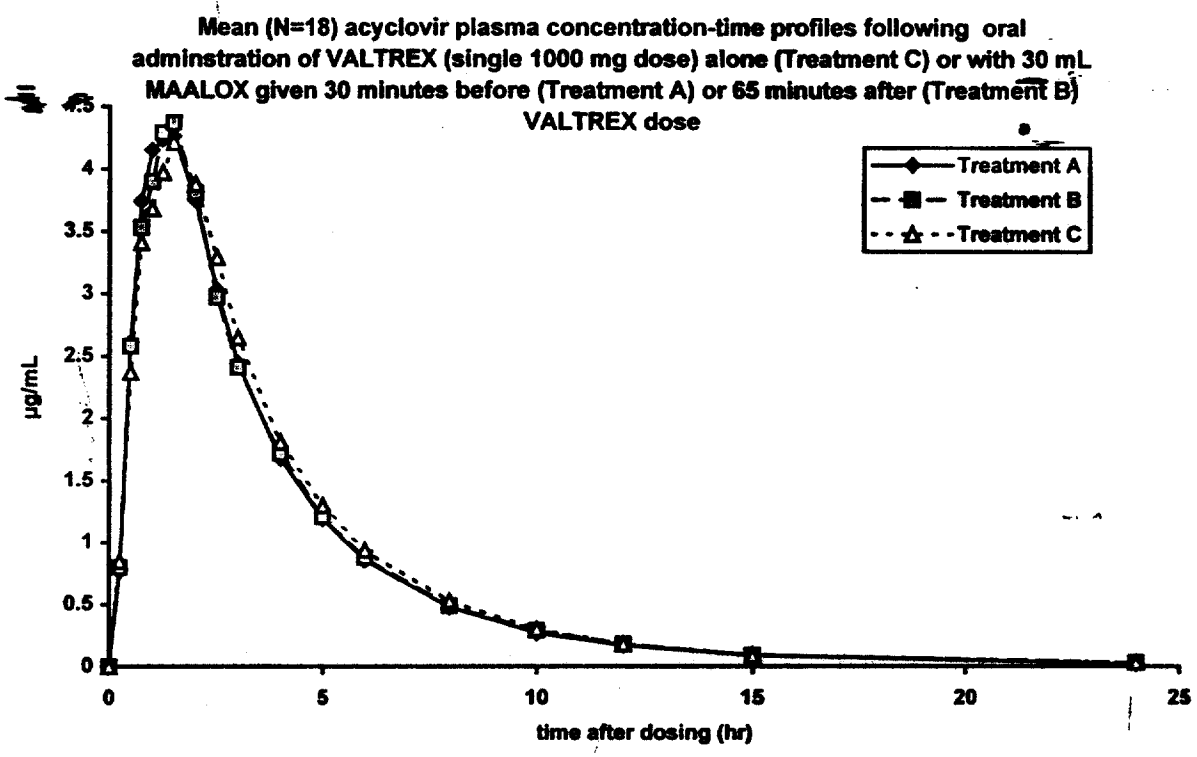
The point estimates and 95% CI for the median difference for T_{max} were:

Acyclovir, median difference and 95% confidence interval for T_{max}
Reference = 1000 mg valacyclovir; Test = 1000 mg valacyclovir + MAALOX 65 minutes after valacyclovir dose

Parameter	Median difference	95% CI
T_{max}	0	-.5-0.25

There were no statistically significant differences between the pharmacokinetic parameters of valacyclovir given with MAALOX® compared with the pharmacokinetic parameters of valacyclovir given alone.

The following figure compares the acyclovir concentration-time profiles in the three treatment groups:



Discussion: The doses of valacyclovir (1000 mg) and MAALOX® (30 mL) investigated in this study are clinically relevant. One recommended VALTREX® regimen (herpes zoster) is 1000 mg q8h for 7 days. The recommended MAALOX® dosage is 10-20 mL, four times a day. Treatments A and B were designed to maximize the effects of MAALOX® on acyclovir kinetics; in Treatment A, valacyclovir was given at the time of peak antacid release in the GI system, and in Treatment B, MAALOX® was given at the acyclovir T_{max} (presumably corresponding to the time of peak valacyclovir absorption).

The acyclovir pharmacokinetic parameters in patients from Study 123-038 were comparable to those previously reported for 1000 mg valacyclovir administered as a single dose (ClinPharm/Biopharm Review of NDA 20-487). Since acyclovir pharmacokinetics when MAALOX® was given either 30 minutes before or 65 minutes after valacyclovir were comparable to acyclovir pharmacokinetics when valacyclovir was given alone, it appears that the gastric pH changes resulting from a 30 mL dose of MAALOX® have no effect on acyclovir bioavailability from an oral dose of valacyclovir.

Summary and Conclusion: MAALOX® given either 30 minutes prior to or 65 minutes following valacyclovir administration had no effect on acyclovir bioavailability from valacyclovir. Thus, no time interval is required between valacyclovir and an antacid administration when given concomitantly. It is recommended that these data be summarized in the VALTREX® package insert.

III. PLASMA ACYCLOVIR CONCENTRATIONS IN PIVOTAL TRIAL

Study RM1996/00228/00: PHARMACOKINETIC EVALUATION OF PLASMA ACYCLOVIR CONCENTRATION MONITORING DATA FROM STUDY 123-026: A COMPARATIVE TRIAL OF VALACYCLOVIR PLUS ACYCLOVIR AND PLACEBO FOR THE SUPPRESSION OF RECURRENT GENITAL HERPES INFECTIONS IN IMMUNOCOMPETENT PATIENTS (NDA 20-550 SE1-003, Vol. 8.4, pp. 14-347).

Objective: Pharmacokinetic analysis of acyclovir concentration monitoring data from Study 123-026. The objective of Study 123-026 was to compare the safety and efficacy of 4 dosage regimens of oral valacyclovir with oral acyclovir and placebo for the suppression of recurrent episodes of genital herpes simplex virus (HSV) infection in immunocompetent patients.

Subjects: 1479 patients with a history of recurrent genital herpes. Individual subject demographics are presented in Appendix I.

Investigators: 53 study sites in the US, Europe, and Australia.

Study Design: Randomized, double-blind, multi-center, multi-national, parallel group, six-arm Phase III study. Patients were randomized to the following groups: valacyclovir mg q12h (N=274); valacyclovir 1000 mg q24h (N=269); valacyclovir 500 mg q24 h (N=266), valacyclovir mg q24h (N=269); acyclovir 400 mg twice daily (N=267); or placebo (N=134). Treatment was for 52 weeks. The regimen of ZOVIRAX® 400 mg q12h for up to 12 months is approved for the chronic suppressive therapy of recurrent genital herpes.

Formulations: Marketed VALTREX® 500 mg tablets (BIN Nos. 2U2776, 3S2769, 1Z2704), marketed ZOVIRAX® 400 mg tablets (3P2789), and investigational valacyclovir mg tablets (3O2783, 4R2769).

Sampling: At months 3, 6, 9 and 12 (end of study), blood samples were collected at random times for the determination of plasma acyclovir concentrations. The exact time and date of each sample was recorded. The dates and times of administration of the two most recent doses of drug (or placebo) were recorded in the case report form.

Assay:

Pharmacokinetic Analysis: A rigorous population pharmacokinetic analysis of the data is planned. For the purposes of submission NDA 20-550 SE1-003, to characterize representative acyclovir concentration-time profiles for patients in the acyclovir and valacyclovir groups, actual post-dose sampling times determined for the monitoring data were rounded to sample collection times used in previous Phase I pharmacokinetic studies of acyclovir and valacyclovir (0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 hr post-dose). Acyclovir concentrations below the LLOQ were assigned values of 0. AUC was calculated by trapezoidal approximation.

Statistical Analysis: Descriptive statistics, including median, mean, standard deviation, coefficient of variation, and minimum and maximum, were determined for acyclovir concentrations at each time point for each active treatment regimen. Statistics were calculated after exclusion of outliers (using the Grubbs test).

Results: The concentration-time data were used to estimate acyclovir exposure from each of the valacyclovir and acyclovir dosing regimens. Summary descriptive statistics for acyclovir concentrations at the various regimens are presented in Table 1 (attached). Estimates of peak acyclovir concentration (C_{max}) and systemic exposure (daily AUC) for the different active drug regimens are presented below:

Drug Regimen	Daily AUC (μg*hr/mL)	C_{max} (μg/mL)	C_{min} (μg/mL)
Valacyclovir mg q12h	12.39	1.57	0.10
Valacyclovir 1000 mg q24h	18.13	5.13	0.04
Valacyclovir 500 mg q24h	10.35	2.48	0.02
Valacyclovir mg q24h	4.95	1.36	0.01
Acyclovir 400 mg q12h	7.60	0.67	0.10

The acyclovir pharmacokinetic estimates are consistent with data from Phase I studies of acyclovir and valacyclovir in healthy adults.

Discussion: All of the valacyclovir dosing regimens were significantly better than placebo in preventing or delaying recurrences of genital HSV during the one-year study period. A clear dose-response relationship was seen across the three once-daily valacyclovir dosing regimens. Valacyclovir 500 mg once daily provided adequate clinical efficacy for most patients, but those with a history of more than 9 recurrences a year appeared to require an alternative dose of 1000 mg once daily or mg twice daily. For the once-daily regimens, the increasing peak concentrations and AUCs of acyclovir associated with increasing valacyclovir doses are consistent with the efficacy dose-response profile. However, the comparable efficacy results observed between the valacyclovir 1000 mg once-daily, valacyclovir mg twice-daily and acyclovir 400 mg twice daily regimens are not explained on the basis of peak acyclovir concentrations nor plasma acyclovir daily AUCs. As can be seen in the attached simulation on page 5 of this review, it may be that a measure such as time duration that acyclovir concentrations exceed a threshold (such as *in vitro* IC_{50} or trough concentrations from the acyclovir twice-daily regimen) may best account for efficacy in suppression of recurrent episodes of genital herpes.

Summary and Conclusion: Plasma acyclovir concentrations were monitored in the blinded, multi-center, placebo-controlled Phase III Study 123-026, in which various acyclovir and valacyclovir regimens were administered for 52 weeks to compare suppression of recurrent episodes of genital herpes. Regimens compared were acyclovir 400 mg q12h, valacyclovir at 500, or 1000 mg q24 hr, valacyclovir at mg q12h. Estimates of acyclovir systemic exposure from the different acyclovir and valacyclovir treatments were consistent with previous Phase I pharmacokinetic data. The efficacy results in this study were not entirely explained by differences in systemic acyclovir peak concentration or daily AUC, but may be best accounted for by the time duration that plasma acyclovir concentrations exceed some threshold level (such as IC_{50}).

Table 1 -- Descriptive Statistics for Acyclovir Concentration (μg/mL) Monitoring Samples

Time (hr)	N	Median	Mean	SD	%CV	Minimum	Maximum
Valacyclovir mg Twice Daily							
0.00	4	0.95	0.77	0.52	67		
0.25	10	0.18	0.67	0.75	112		
0.50	15	1.16	1.26	1.20	95		
0.75	17	1.57	1.83	1.17	64		
1.00	37	1.51	1.60	1.09	68		
1.50	69	1.46	1.54	0.83	54		
2.00	45	1.28	1.35	0.83	61		
2.50	38	0.81	0.92	0.64	70		
3.00	52	0.90	0.99	0.47	47		
3.50	33	0.68	0.82	0.46	57		
4.00	48	0.71	0.72	0.41	56		
5.00	55	0.48	0.51	0.34	67		
6.00	56	0.32	0.33	0.17	52		
8.00	55	0.18	0.19	0.12	61		
10.00	78	0.14	0.15	0.09	57		
12.00	43	0.09	0.10	0.06	61		
Valacyclovir 1000 mg Once Daily							
0.00	1	0.03	0.03	.	.		
0.25	9	0.40	1.22	1.78	146		
0.50	12	2.00	2.23	1.65	74		
0.75	21	2.77	2.97	2.64	89		
1.00	39	5.13	4.36	3.29	76		
1.50	57	3.07	3.86	3.09	80		
2.00	57	3.52	3.78	2.38	63		
2.50	33	3.72	4.57	2.73	60		
3.00	47	3.35	3.47	2.75	79		
3.50	34	2.49	2.87	2.05	71		
4.00	45	1.86	2.45	1.90	77		
5.00	53	1.31	2.15	2.15	100		
6.00	68	1.02	1.15	0.80	69		
8.00	71	0.64	0.71	0.52	74		
10.00	62	0.34	0.40	0.29	73		
12.00	42	0.10	0.14	0.14	97		
16.00	31	0.03	0.04	0.03	87		
20.00	15	0.02	0.02	0.02	92		
24.00	3	0.05	0.04	0.024	8		

Table 1 -- Descriptive Statistics for Acyclovir Concentration (μg/mL) Monitoring Samples (continued)

Valacyclovir 500 mg Once Daily

Time (hr)	N	Median	Mean	SD	%CV	Minimum	Maximum
0.00	5	0.25	0.23	.12	51		
0.25	10	0.18	0.32	0.35	110		
0.50	15	2.07	1.94	.43	74		
0.75	13	2.14	2.02	1.79	89		
1.00	38	1.81	1.94	1.47	76		
1.50	59	2.48	2.43	1.62	66		
2.00	50	2.31	2.18	1.21	55		
2.50	38	2.03	2.06	1.32	64		
3.00	40	1.70	1.66	0.96	58		
3.50	26	1.45	1.89	1.29	68		
4.00	46	1.03	1.30	1.11	86		
5.00	55	0.83	0.80	0.53	66		
6.00	59	0.46	0.49	0.36	73		
8.00	78	0.32	0.34	0.20	59		
10.00	78	0.17	0.19	0.17	90		
12.00	45	0.03	0.05	0.06	106		
16.00	19	0.01	0.02	0.03	135		
20-00	10	0.02	0.05	0.07	156		
24.00	8	0.02	0.02	0.01	69		

Valacyclovir mg Once Daily

Time (hr)	N	Median	Mean	SD	%CV	Minimum	Maximum
0.00	1	0.17	0.17	.	.		
0.25	14	0.12	0.34	0.44	129		
0.50	12	0.16	0.85	1.17	139		
0.75	20	0.76	1.05	1.05	100		
1.00	37	1.20	1.39	0.94	68		
1.50	71	1.36	1.23	0.81	66		
2.00	46	1.13	1.16	0.69	59		
2.50	48	1.12	1.03	0.56	55		
3.00	23	0.64	0.83	0.63	76		
3.50	29	0.55	0.58	0.38	65		
4.00	46	0.69	0.71	0.43	61		
5.00	41	0.37	0.35	0.25	70		
6.00	56	0.26	0.29	0.16	56		
8.00	61	0.12	0.14	0.10	75		
10.00	84	0.08	0.08	0.07	82		
12.00	51	0.01	0.03	0.04	1??		
16.00	23	0.00	0.01	0.01	167		
20.00	12	0.00	0.00	0.00	234		
24.00	3	0.01	0.01	0.01	100		

Table 1 -- Descriptive Statistics for Acyclovir Concentration (μg/mL) Monitoring Samples (continued)

	Acyclovir 400 mg Twice Daily					
Time (hr)	N	Median	Mean	SD	%CV	Minimum	Maximum
0.00	6	0.15	0.16	0.11	72		
0.25	11	0.13	0.21	0.17	79		
0.50	16	0.23	0.47	0.50	105		
0.75	14	0.67	0.74	0.59	80		
1.00	39	0.64	0.59	0.30	51		
1.50	38	0.54	0.55	0.28	51		
2.00	52	0.62	0.58	0.32	55		
2.50	31	0.64	0.66	0.34	52		
3.00	39	0.58	0.56	0.32	57		
3.50	33	0.59	0.57	0.27	39		
4.00	32	0.36	0.47	0.31	66		
5.00	58	0.38	0.41	0.20	50		
6.00	94	0.24	0.27	0.16	60		
8.00	64	0.17	0.25	0.17	67		
10.00	82	0.14	0.13	0.07	50		
12.00	61	0.09	0.10	0.05	53		

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pages of trade secret and/or confidential commercial information

V. LIST OF SUBMITTED STUDIES NOT REVIEWED

1. Comparative estimates of systemic acyclovir exposure from selected dosing regimens of intravenous and oral ZOVIRAX® and from oral VALTREX® administration (NDA 20-550 SE1-003, Vol. 8.4, pp. 1-12). *Reason why not reviewed*: The dosing regimens used for these estimates are not the same as those evaluated in pivotal trial 123-026.
2. Pharmacokinetic evaluation of plasma acyclovir concentration monitoring data from Study 123-037: a randomized, double-blind, controlled study of valacyclovir for the suppression of recurrent genital herpes simplex virus infection in immunocompetent patients (NDA 20-550 SE1-003, Vol. 8.4, pp. 348-499). *Reason why not reviewed*: This study investigated only one dosing regimen (VALTREX® 500 mg q24h) and does not add any additional information to the pharmacokinetic estimates obtained from Study 123-026, which compared 5 dosing regimens, including VALTREX® 500 mg q24h.

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VI. LABELING COMMENTS

The following comments refer to the attached draft package insert.

Drug Interaction, pages 6-7

DELETE lines 116-133

REPLACE with following text:

"Digoxin pharmacokinetics were not affected by multiple-dose administration of VALTREX 1 gram three times daily. No changes in acyclovir pharmacokinetics were observed following single-dose administration of 1 gram valacyclovir with antacids or digoxin or following multiple-dose administration with thiazide diuretics. An additive increase in acyclovir AUC and C_{max} was observed when VALTREX was administered to healthy volunteers who were taking cimetidine, probenecid, or a combination of both cimetidine and probenecid."

PRECAUTIONS, Drug Interactions, page 11

DELETE lines 214-219.

Table 3, page 18:

CHANGE dosing recommendations (last column of table) for renally impaired subjects as follows:

Creatinine Clearance (mL/min)	Suppressive therapy
$\geq$ 50	1000 mg every 24 hr
30-49	1000 mg every 24 hr
10-29	500 mg every 24 hr
< 10	500 mg every 24 hr

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20550/S-003

ADMINISTRATIVE DOCUMENTS

ITEM 13

Patent Information Pursuant to 21 U.S.C. 355 for

VALTREX® (valacyclovir hydrochloride) Caplets

NDA 20-550

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

Trade Name:	Valtrex® Caplets
Active Ingredient:	Valacyclovir hydrochloride
Strength(s):	500 mg and 1 gm
Dosage Form:	Caplet
NDA Number:	20-550
Approval Date:	December 15, 1995

Applicable Patent Numbers and Expiration Dates:

Patent No.	4,957,924
Expires:	August 4, 2008
Owner:	Glaxo Wellcome Inc.
Type:	Composition Formulation Method of Use (Suppression of genital herpes virus infections)
Patent No.	4,567,182
Expires:	January 28, 2003
Patent Owner:	Co Pharma Corporation s.r.l., Genoa, Italy (license owned by Glaxo Wellcome Inc.)
Type:	Composition

The undersigned declares that U.S. Patent No. 4,957,924 covers the composition, formulation, and method of use of VALTREX® (valacyclovir

hydrochloride) Caplets and U.S. Patent No. 4,567,182 covers valacyclovir. These U.S. patents should be included in Item 13 of NDA 20-550.

November 7, 1996
Date

Karen L. Prus
Karen L. Prus, Ph.D.
Patent Attorney
Registration No. 39,337

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EXCLUSIVITY SUMMARY FOR NDA # 20-550 SUPPL # 003

Trade Name Valtrex® GenericName: valacyclovir

Applicant Name Glaxo Wellcome HFD # 530

Approval Date If Known: September 26, 1997

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 question 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.) SE1

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?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8 (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 /___/ NO /_X_/

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

NDA# _____ _____

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 /___/

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 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /___/ 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 8:

_____

_____

(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 /___/

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:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 YES /___/ NO /___/

Investigation #2 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:

_____ _____

_____ _____

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 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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"):

_____

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 /___/ ! 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 /___/

If yes, explain: _____

_____

T Cwetkovich MD
Signature
Title: Medical Officer

9/29/97
Date

Debra Griffin MD
Signature of Office/
Division Director
(Acting)

9/24/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA)/PLA/PMA # 20-550 Supplement # 003 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HF 530 Trade and generic names/dosage form: Valtrex/valacyclovir Action: (AP) AE NA
Caplets 500mg and 1gm

Applicant Glaxo Wellcome Therapeutic Class Antiviral/anti-herpetic

Indication(s) previously approved Herpes zoster, intial episode and treatment of genital herpes.
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application Suppression of genital herpes (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

X a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

X c. The applicant has committed to doing such studies as will be required.
- X (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

T Quetkowichmd 8/10/97

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-550/S-003
HFD-530/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/10/97)

Valtrex® (valacyclovir hydrochloride) Caplets
NDA 20-550 Supplement

Debarment Certification:

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated July 29, 1992 from Daniel L. Michels, Office of Compliance at FDA, Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not use in any capacity the services of any person debarred under section 306 (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Richard Holzenkamp for
David Savello

David R. Savello, Ph.D.
Vice President, Regulatory Affairs

31/Oct/96
Date