CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-550/S-012

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW
NDA 20-550 (S-012)

Date Submitted: August 30, 2000

Date Received: August 31, 2000

Date Assigned: September 9, 2000

Date review completed: January 9, 2001

Date revisions completed: March 13, 2001

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

Drug:

Generic: Valacyclovir hydrochloride

Trade: Valtrex ®

Chemical: *L* -valine, 2-[(2-amino-1,6-dihydro-6-oxo-9 *H* -purin-9-yl)methoxy]ethyl ester, monohydrochloride.

Dosage form: 500 mg caplets

Route of administration: Oral

Proposed Indication: Treatment of recurrent genital herpes

RESUME

The results of one double-blind, randomized clinical trial (HS2A4004) in immunocompetent patients 18 years of age and older with recurrent genital herpes was submitted by the applicant. Valacyclovir 500 mg po BID for 3 days was compared with the currently approved regimen of valacyclovir 500 mg po BID for 5 days. The primary efficacy endpoint measured was time to lesion healing. Other efficacy parameters assessed included duration of pain, length of episode, halted progression of lesions and severity of pain.

No difference in time to lesion healing, duration of pain or length of episode was noted between the 5-day and 3-day regimens. Valacyclovir had an acceptable safety profile in the population studied. Based on these findings, valacyclovir 500 mg po BID for 3 days should be approved for the treatment of recurrent genital herpes in healthy individuals 18 years of age and older.

BACKGROUND

Valacyclovir is the hydrochloride salt of L-valyl ester of acyclovir. The currently approved dosage of valacyclovir for the treatment of recurrent genital herpes in immunocompetent adults is 500 mg po BID for 5 days. This indication was based on the results of two clinical trials evaluating valacyclovir in immunocompetent patients for the treatment of recurrent genital herpes. In the first study (34-526-004), time to lesion healing was similar in patients who received valacyclovir 1000 mg po BID for 5 days or acyclovir 200 mg po five times a day for 5 days. In the second study (34-526-028), valacyclovir (500 mg po BID or 1000 mg po BID for 5 days) was compared with placebo. Patients who received valacyclovir 1000 mg or 500 mg po BID for 5 days had a shorter time to lesion healing compared to placebo. Treatment with valacyclovir 500 mg po BID was comparable to treatment with valacyclovir 1000 mg po BID for 5 days.

Materials reviewed

Volumes 1-10; 40 case report forms submitted electronically.

PRE-CLINICAL STUDIES

Chemistry/Manufacturing control

No new studies were submitted.

Animal pharmacology/toxicology

No new studies were submitted.

Microbiology

No new studies were submitted.

Pharmacokinetics

No pharmacokinetic studies were performed.

SUMMARY OF CLINICAL STUDY HS2A4004

Title: A comparison of oral Valtrex® 500 mg twice daily for three or five days for treatment of recurrent genital herpes.

Objective: To evaluate the efficacy and safety of oral valacyclovir 500 mg twice daily for 3 days compared to valacyclovir 500 mg twice daily for 5 days.

Study Centers: 34 centers in the United States and 14 centers in Canada.

Study Period: November 1996- June 1997.

Design: This was a multi-center, randomized, double-blind clinical trial comparing the efficacy and safety of valacyclovir for the episodic treatment of recurrent genital herpes infection in immunocompetent adults. Patients with a history of recurrent genital herpes self-initiated therapy with valacyclovir 500 mg twice a day. They were then stratified by gender and randomized to two treatment groups, to receive either valacyclovir 500 mg

twice daily for five days or valacyclovir 500 mg twice daily for three days and matching placebo twice daily for two additional days.

Study population: To be eligible for enrollment, patients had to be otherwise healthy and 18 years of age and older with a history of at least 4 episodes of recurrent genital herpes in 12 months or 2 episodes in 6 months involving genital, perianal or closely related sites like buttocks. Patients who had received suppressive therapy with acyclovir for recurrent genital herpes during the last 12 months, must have experienced at least one recurrent episode within three months of discontinuing suppressive therapy and within three months of study enrollment.

Patients were required to have adequate documentation of prior herpes infections. The following were considered adequate documentation: positive herpes simplex culture result, direct antigen tests, Tzanck smears, immunofluorescence assay or written confirmation of genital herpes by a primary care physician.

Patients with protocol-defined hepatic or renal impairment, women of child bearing potential not employing adequate contraception, pregnant or nursing women, immunocompromised patients, patients currently receiving probenecid, systemic antiviral therapy or immunomodulatory treatment or who are currently receiving or who had received an investigational drug in the 30 days prior to this study were excluded.

ENDPOINTS

Primary Efficacy Measure

- **Time to lesion healing:** This was defined as the number of days, rounded to the nearest tenth of a day, between initiation of treatment and complete re-epithelialization of all lesions. Patients with halted progression of lesions were excluded.

Secondary Efficacy Measure

- **Duration of pain:** This was defined as the number of days, rounded to the nearest tenth of a day, from the time of initiation of treatment or start of pain/discomfort, whichever occurred later, to the complete cessation of pain.

Other Efficacy Measures

- **Length of episode:** This was defined as the number of days, rounded to the nearest tenth of a day, between initiation of treatment and complete resolution of all symptoms and signs.

- **Halted progression of lesions:** Patients whose lesions did not progress past the macule/papule stage and who had clinical symptoms, but did not develop lesions.

PROCEDURES

At the screening visit, a three-day supply of open-label valacyclovir 500 mg was dispensed. Patients were instructed to initiate treatment at the first sign or symptom of a genital herpes recurrence and to return to clinic within 24 hours of initiating therapy. At this visit they were stratified by gender and randomly assigned to one of the two

treatment groups, valacyclovir 500mg po BID or placebo, for the final two days of dosing.

Patients were evaluated in the clinic daily for six consecutive days and twice weekly thereafter until all lesions had healed and clinical symptoms were absent. Clinical assessment at each visit included lesion staging (prodrome, macule/papule, vesicle/pustule/ulcer, crust, healed) and pain/discomfort (none, mild, moderate, severe) assessment.

Swabs for viral culture were obtained on Study Day 1, in patients who did not have a positive HSV culture or HSV-2 specific Western blot assay documented in their history. HSV was identified by cytopathic effect; virus typing was not performed.

Patients maintained daily diary cards in which they recorded medication taken and their assessment of lesion healing and pain and /or discomfort. At each clinic visit, data from the diary cards was reviewed and transferred to the case report forms. The investigator resolved inconsistent information. Adverse events and dosing compliance were also assessed at the clinic visit.

Safety Assessment

Clinical chemistry (creatinine, alkaline phosphatase and ALT) and hematology testing (hemoglobin, white blood cell and platelet count) was performed at screen and on study days 1 and 6. Serum pregnancy test was performed on all female patients of childbearing potential at screen and on study day 1.

All adverse experiences were categorized by maximum intensity, seriousness and causality and tabulated for each treatment group. Occurrence of thrombotic thrombocytopenic purpura and/or hemolytic uremic syndrome was monitored.

STATISTICAL CONSIDERATIONS

Sample size

A target enrollment of 920 patients was designed to accrue 606 treated patients of whom at least 400 patients would develop a lesion and thereby be evaluable for lesion healing. With a sample size of 400 patients, the study had a power of 80% to establish that the median difference in treatment was less than 0.7 days. The value of 0.7 days was chosen as a conservative estimate of a 20% difference from the 5-day median healing time. The planned 606 treated patients provided at least 80% power to establish equivalence in the median length of episode and median duration of pain.

Covariates

Gender and analysis centers were included in the Cox's proportional hazard models for lesion healing time and length of episode. Large study sites defined by the number of patients randomized, the distribution of gender, and the treatment groups were treated as separate centers and the smaller sites were combined into one large center. Additional exploratory analyses were performed on the intent-to-treat group (ITT) group for two end points: time to lesion healing and length of episode. The factors investigated were age, annual number of recurrences, pain severity at baseline, and time since first sign or symptom to initiation of therapy.

Analysis

The ITT group was defined as all randomized patients. Patients with halted progression of lesions were excluded from the ITT subset for time to lesion healing endpoint. An efficacy subset was defined as all patients in the ITT group who did not have any of the defined protocol violations and had a time to event endpoint.

Equivalence was assessed primarily with a Hodges-Lehman 95% confidence interval about the median treatment difference for time to lesion healing, duration of pain, and length of episode.

Supportive analyses of time to lesion healing, duration of pain and length of episode were performed using Kaplan-Meier product limit estimation and the Cox proportional hazards model, controlling for gender and analysis center. Analysis of the proportion of patients with halted progression of lesions and analysis of pain severity utilized the Cochran-Mantel-Haenszel test.

For the primary endpoint only, treatment differences were examined in the following subgroups: Age (≤ 35 years, >35 years), Gender (Male, Female) and Race (White, Non-white). All statistical tests were two-sided and at 0.05 level of significance.

RESULTS

Patient Disposition

Of the 1,170 patients enrolled, 800 were randomized following a recurrence of genital herpes and the remaining 370 were classified as enrolled but not randomized.

Table 1 describes the demographics of both randomized and non-randomized patients. Sixty-three percent of patients were female, the age range was from 18-74 years (median 34) and 18-82 years (median 35) in the 5-day and 3-day arm respectively. Most patients were White (84% and 85%), with Blacks and persons of other races comprising 16% and 15% of the 5-day and 3-day group respectively.

Table 1: Patient Demographics

Characteristic	Not randomized	Treatment Group	
		VACV-5 days	VACV-3 days
Median age (Min-Max) (Years)	37 (18-74)	34 (18-74)	35 (18-82)
Gender			
Female N (%)	203 (55%)	252 (63%)	253 (63%)
Male N (%)	167 (45%)	146 (37%)	149 (37%)
Race			
Caucasian	317 (86%)	335 (84%)	343 (85%)

Characteristics of prior HSV infections among the three groups of patients are presented in Table 2. More patients in the ITT group had ≥ 9 recurrences in the past year and were more likely to have received previous acyclovir therapy compared to the enrolled but not randomized group. More patients in the 5-day group had ≥ 9 recurrences in the past 12 months compared to the 3-day group.

Prior herpes infection was documented in 99% and 92% of the ITT and not randomized groups respectively ($p<0.001$). Involvement of extra-genital sites was similar in the two groups.

Table 2: Characteristics of previous HSV infections

Characteristic	Not randomized	Treatment Group	
		VACV-5 days	VACV-3 days
Recurrences in last 12 months			
1-3	22 (6%)	21 (5%)	21 (5%)
4-8	277 (75%)	252 (63%)	272 (68%)
≥ 9	71 (19%)	125 (31%)	109 (27%)
Suppressive treatment in last year	22 (6%)	38 (10%)	32 (8%)
Prior HSV documented	341 (92%)	391 (98%)	397 (99%)
Extra genital herpes	108 (29%)	119 (30%)	116 (29%)

Screening physical examination and baseline laboratory tests were similar in the two treatment groups, except for one patient in the 3-day treatment group who had Wolf-Parkinson-White syndrome.

COMMENTS

More women than men were enrolled and also randomized. However, the proportion of women in the two treatment arms was comparable. Patients with ≥ 9 recurrences were more likely to have a recurrence during the study period and were hence more likely to be randomized.

Accountability of all patients enrolled in the study is shown in Table 3.

Table 3: Patient Accountability

Characteristic	Not randomized	VACV-5days	VACV-3days
Completed study	0	362 (91%)	359 (89%)
Premature termination	370	36	43
Enrolled, not treated	293	0	0
Consent withdrawn	10	2	2
Lost to follow-up	35	3	6
Protocol violation	32	31	35

Seventy-nine subjects (10%) in the ITT group withdrew from the study and nine subjects were lost to follow up.

Of the 800 randomized patients, 157 (89 and 68 in the 5-day and 3-day arm respectively) had major protocol deviations/violations. A summary of the major protocol

violations is given in Table 4 *. Patients with no major protocol violations comprised the efficacy subset.

Table 4: Protocol violators

Violation	VACV-5days	VACV-3days
No evidence of genital herpes	6	5
Failed to initiate treatment in 24 hours	43	24
Failed to take ≥ 80% of study medication	7	2
Failed to initiate treatment with correct dose	2	1
Took antiviral or immunomodulatory medications	17	12
Other	25	30

*A single patient may have violated protocol for more than one reason, and is counted for each violation.

COMMENTS

Reasons for protocol violation in the "other" category were analyzed, based on a listing provided by the applicant. In 11 patients, mistiming of Day 1 visit was the reason for protocol violation and in 16 patients the Day 2-6 visits were mistimed/patient was non-compliant.

RESULTS OF EFFICACY ANALYSIS

Results of analyses of the ITT population are presented. Analysis of the efficacy subset for the primary efficacy endpoint was performed and was similar to the ITT group. None of the exploratory analyses were contributory and therefore will not be presented. Center effects will not be discussed, as important differences between center-stratified analyses were not detected.

Out of the 800 randomized patients, 592 developed lesions and were assessed for time to lesion healing. Two hundred and eight patients had halted progression of lesions. One patient had a missing endpoint, so 591 patients constituted the ITT population for time to lesion healing. Analyses of the ITT population for duration of pain and length of episode were based on 799 patients.

Out of the 592 patients, 120 had violated the protocol, so 472 patients comprised the efficacy subset.

The median days, median difference and its 95% confidence limits, hazard ratios and their 95% confidence limits for the different endpoints for both treatment groups are presented in Table 5.

Table 5: Efficacy endpoints

Endpoint	Median days		Median Difference	95% CI	Hazard Ratio	95% CI
	VACV-5 days	VACV-3 days				
Time to lesion healing	4.7	4.4	0.1	-0.1, 0.4	0.95	0.81, 1.13
Duration of pain	2.5	2.9	-0.1	-0.5, 0.0	1.15	0.996, 1.33
Length of episode	4.4	4.3	0.0	-0.2, 0.2	1.05	0.91, 1.22

Time to lesion healing

Data on time to lesion healing were available for 591 patients; 208 patients had halted progression of lesions and one patient was excluded due to a missing endpoint. Median time to lesion healing and the hazard ratio were similar in the two treatment groups. Eight (1.35%) patients had censored time to lesion healing.

Duration of pain

Data on duration of pain was available for 799 patients. Data for one patient in the 3-day treatment group was deleted. Median duration of pain and the hazard ratio were similar in the two treatment groups.

Length of Episode

Data on length of episode was available for 799 patients. Data for one patient in the 3-day treatment group was deleted. Median length of the episode and the hazard ratio were similar in the two treatment groups.

Halted progression of lesions

Lesions did not progress past the macule/papule stage in 26.6% and 25.4% of patients in the 5-day and 3-day treatment groups respectively. No significant differences were observed between the two groups in the proportion of patients with halted progression of lesions.

Pain severity

Proportion of patients with pain in each category of severity was similar in the two groups. No statistical association of severity of pain and treatment groups was seen on study days 3 and 5.

EVALUATION OF SAFETY

Deaths

No deaths occurred in the study population.

Serious adverse events

No serious adverse events were reported.

Treatment-limiting adverse events

One patient in the 3-day treatment group developed a treatment-limiting adverse event. This patient reported three adverse experiences (diarrhea, dizziness and diaphoresis). Treatment was interrupted for one day and the patient subsequently completed the study.

All adverse events

Headache, nausea, diarrhea, fatigue, dizziness and colic were reported by ≥ 2% of patients in either group. Similar proportions of patients in both groups reported these adverse events.

Pregnancies

One patient was found to be pregnant. After completion of the study she voluntarily terminated her pregnancy.

Laboratory abnormalities

The descriptive statistics (mean, median, minimum, lower quartile, upper quartile and maximum) including Hodges Lehman estimates and 95% confidence intervals revealed no differences between the two treatment groups with regard to clinical chemistry and hematology parameters. Quartile plots of the data and change from screen quartile plots for these tests showed no important treatment effects or trends over time.

CONCLUSIONS

Immunocompetent adults with recurrent genital herpes, treated with valacyclovir 500 mg po BID for 3 days, had resolution rates similar to those treated with valacyclovir 500 mg po BID for 5 days. No significant differences were observed between the two groups with respect to the efficacy endpoints, i.e. time to lesion healing, duration of pain, length of episode, halted progression of lesions and severity of pain.

There were no significant differences between randomized and non-randomized patients or between the two treatment groups with regards to demography, baseline characteristics or screening physical examination.

More women than men were enrolled and subsequently randomized. Prior HSV infection was better documented in the randomized group. Adverse events were mild and did not require discontinuation of the study medication. Study drug compliance was comparable in the two treatment groups. No clinically important changes in the laboratory parameters were observed during the study period.

REGULATORY ACTION

Based on information submitted in NDA 20-550 (SLR-012), the application for oral valacyclovir 500 mg BID for 3 days for the treatment of recurrent genital herpes in immunocompetent adults should be approved.

Sumathi Nambiar, M.D.
Medical Officer, Division of Antiviral Drug Products

Concurrences:
HFD-530/Div Dir/DBirnkrant
HFD-530/TL/TCvetkovich

CC:
HFD-530/NDA 20-550
HFD-530/DivFile
HFD-530/Biopharm/
HFD-530/PharmTox/
HFD-530/Micro/
HFD-530/Chem
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/s/

Sumathi Nambiar
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Therese Cvetkovich
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRAL DRUG PRODUCTS

Memorandum

Date: May 24, 2001

To: NDA 20-550

From: Sumathi Nambiar, M.D. Medical Officer HFD-530

Through: Therese Cvetkovich, M.D. Medical Team Leader, HFD-530

Subject: Medical Officer's review of NDA 20-550 SE2-012

Supplement SE2-012 for Valtrex ® (valacyclovir hydrochloride) caplets provides data on the use of Valtrex ® (valacyclovir hydrochloride) caplets 500 mg twice a day for three days compared to 500 mg twice a day for five days in the treatment of recurrent genital herpes. Data provided in this supplement supports a change in the dosing schedule of Valtrex ® (valacyclovir hydrochloride) caplets to 500 mg twice a day for three days in the treatment of recurrent genital herpes.

Please refer to CSO labeling review for changes in the label.

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/s/

Sumathi Nambiar
5/24/01 03:43:35 PM
MEDICAL OFFICER

Therese Cvetkovich
6/6/01 02:02:06 PM
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Debra Birnkrant
6/14/01 10:53:30 AM
MEDICAL OFFICER

34 page(s) of revised draft labeling has been redacted from this portion of the review.

Group Leader Memorandum

NDA:	**20-550**
Drug:	**valacyclovir (Valtrex®)**
Indication:	**Treatment of a recurrence of genital herpes**
Dose:	**500 mg BID for 3 days**
Applicant:	**Glaxo Wellcome, Inc.**
Submission received:	**August 31, 2000**
Date of memorandum:	**May 30, 2001**

In this supplemental NDA submission the applicant requests approval of a three day regimen of valacyclovir for the treatment of a single episode of recurrent genital herpes. A previously approved regimen was five days in duration. In support of this request, the applicant submitted the results of a single, double-blind, randomized study in immunocompetant adults in which the five and three day regimens were compared. The primary efficacy endpoint was the time to lesion healing. No differences between the two regimens were detected and evaluation of secondary endpoints such as length of episode or duration of pain supported this finding. No new safety issues were identified.

I concur with the recommendation of Dr. Nambiar, the primary medical reviewer, that this application should be approved. There were no outstanding issues related to this approval.

/S/

Therese Cvetkovich, M.D.
Medical Team Leader, DAVDP