

## **MEMORANDUM**

**DATE:** April 14, 2003

**TO:** Advisory Committee Members and Guests

**FROM:** Valacyclovir Review Team

**THROUGH:** Debra Birnkrant, M.D.  
Division Director  
Division of Antiviral Drug Products (DAVDP)

**SUBJECT:** Background Package for Antiviral Drugs Advisory Committee Meeting of May 14, 2003; NDA 20,550/S-019  
Valtrex® (valacyclovir hydrochloride) 500 mg once daily for the reduction of transmission of genital herpes between herpes simplex type 2 discordant heterosexual couples

This document provides background information on material scheduled for presentation and discussion at the upcoming advisory committee meeting. On May 14, 2003, the advisory committee will be asked to provide advice on the use of valacyclovir caplets for the reduction of transmission of genital herpes among monogamous heterosexual couples. This supplemental new drug application contains data from a single international, randomized, placebo-controlled clinical trial (HS2AB3009) and supporting data from a viral shedding substudy. This application raises a number of important issues including extrapolation of data to other patient populations, impact on public health recommendations, and issues related to the potential for development of resistance when valacyclovir is more widely used.

Specifically, the applicant is seeking the following indication: Valacyclovir 500 mg once daily is indicated to reduce the risk of transmission of genital herpes with the use of suppressive therapy and safer sex practices.

### **Regulatory History**

Valacyclovir, a prodrug of acyclovir, is rapidly converted to acyclovir and has demonstrated antiviral activity against HSV-1, HSV-2, and VZV. Valacyclovir is approved and indicated for the treatment and suppression of genital herpes.

Prior to initiating the clinical trial (HS2AB3009), the sponsor and DAVDP discussed the study design, patient selection criteria, selection of the primary endpoint, the utility of two versus one pivotal trial, and other topics. In 1996, the applicant proposed a randomized, multicenter, double-blinded, placebo-controlled Phase 3 study to evaluate valacyclovir suppressive therapy in the source partner in order to prevent HSV-2 transmission to the susceptible partner in monogamous, heterosexual couples. Initially the sponsor planned to enroll 1500 couples discordant for the presence of HSV-2 antibody at approximately 35 sites in the USA, Canada, and Europe. The seropositive source partner was randomized 1:1 to receive either valacyclovir 500 mg once daily or

placebo for 8 months and monitored for clinical manifestations of genital herpes recurrence. The susceptible partner was monitored for clinical and subclinical acquisition of HSV-2. The randomization was stratified to enroll 2 susceptible-female-partner couples for each susceptible-male-partner couple. The mutually agreed upon primary endpoint was the proportion of couples with clinical evidence of a first symptomatic episode of genital HSV-2 infection in the susceptible partner. The clinical endpoint was to be confirmed by laboratory evidence of HSV-2 infection demonstrated by viral culture, PCR or HSV-2 seroconversion. Secondary endpoints included time to clinical symptoms of genital HSV-2 in the susceptible partner, the proportion of couples with evidence of symptomatic or asymptomatic HSV-2 seroconversion, and time to first recurrence of genital herpes in the source partner.

The DAVDP review team suggested that demonstration of efficacy for this indication would be complicated, and that a single study might be too small and too narrowly focussed. The DAVDP was concerned about subsequent use of valacyclovir in populations not studied in the proposed trial, and the potential for increasing risky sexual practices (less condom usage) resulting in acquisition of other STDs. FDA suggested consideration of two studies, one that would enroll source partners who were candidates for antiviral suppression and another that would enroll source partners who were not considered candidates for suppressive therapy. Two studies with robust results would effectively address many of the potential regulatory concerns and would permit a broader and more substantial indication than would a single, targeted study. The sponsor did not agree to a second study, but acknowledged seeking a labeling change based on the population specifically studied in protocol HS2AB3009.

### **Description of Clinical Trial**

#### Phase 3 clinical trial (HS2AB3009)

The applicant conducted a randomized, double-blind, placebo-controlled trial comparing valacyclovir 500 mg once daily for 8 months to placebo for prevention of HSV-2 transmission in 1,484 HSV-2 discordant, monogamous, heterosexual couples. Due to slow recruitment, the study was expanded with participants enrolled from 94 sites in North America, Australia, Europe and South America. Couples had to be at least 18 years of age and in general good health. Source partners were evaluated monthly and received open-label valacyclovir 500 mg twice daily for 5 days for genital HSV-2 recurrences. The susceptible partner was also monitored monthly for acquisition of HSV-2. In the event that the susceptible partner developed an initial genital HSV-2 episode, open label valacyclovir was provided. All subjects were encouraged to use condoms during each sexual encounter, regardless of other birth control methods used, and to abstain from sex during clinical recurrences.

Criteria for inclusion were monogamous, heterosexual couples, 18 years of age or older, in general good health, and able and willing to comply with the protocol. The source partner had to have positive HSV-2 serum antibody as determined by Western blot and a history of nine or fewer episodes of genital herpes per year. The susceptible partner had to have a negative HSV-2 serum antibody by Western blot at screening.

Subjects were excluded if either partner had a history of compromised immune function or known HIV infection. Women who were pregnant, contemplating pregnancy within one year, currently lactating or of childbearing potential and not using any effective method of contraception were excluded. The source partner was excluded if renal or hepatic function was impaired (serum creatinine > 1.5 mg/dl or creatinine clearance < 30 ml/min or ALT > 3 x ULN), or if HSV-2 resistance to acyclovir, famciclovir, or ganciclovir had been documented. Susceptible partners were also excluded if additional sexual partners were acknowledged.

Source patients were evaluated monthly for study drug accounting, adverse experience reporting, concomitant medication use, and symptoms and recurrences (oral and genital) of HSV as recorded on diary cards. Source partners were required to return to the clinic when experiencing an HSV-2 recurrence. At the time of suspected recurrence source partners would undergo HSV-2 culture, receive a 5-day course of valacyclovir (500 mg bid), record the outcome of recurrence on a diary card, and return to clinic if the recurrence had not resolved within 5 days. They were not asked to report sexual practices or behavior.

Susceptible partners were evaluated monthly for signs and symptoms of primary HSV-2 infection, serum samples for HSV-2 serology were taken, and sexual exposure and practices were reviewed. Susceptible partners were strongly encouraged to visit the clinic within 24 hours of experiencing a possible HSV-2 infection and undergo genital examination. Lesions were swabbed for viral culture and PCR testing and serum samples were obtained for HSV serology at the same time. Symptomatic susceptible partners in the USA and Canada were offered valacyclovir 1 gram twice daily for 10 days; in the rest of the world, symptomatic susceptible partners were offered 500 mg bid for 5 or 10 days.

Two central clinical laboratories were charged with detection and quantitation of HSV-2 markers. All specimens for viral culture from Canadian subjects were to be sent to a laboratory in Vancouver. All specimens for viral culture from the rest of the world were to be sent to a laboratory in Seattle. The Seattle laboratory also conducted all PCR and HSV-2 serology studies. The two central clinical laboratories used different methods for HSV-2 culture. An unspecified number of samples arrived at the laboratories “unlabeled, incorrectly labeled, contaminated, or were deemed unanalyzable due to improper transport or other conditions.”

The agreed-upon primary endpoint was the proportion of couples with clinical evidence of a first episode of genital HSV-2 in the susceptible partner, defined as symptomatic HSV-2 infection confirmed by culture, PCR, or HSV-2 seroconversion. An Endpoint Committee (EPC) was formed to evaluate all endpoint cases submitted by study investigators prior to unblinding. The EPC was composed of five external experts in genital herpes research. A treatment failure was defined as a susceptible partner who had signs/symptoms of HSV-2 infection confirmed by viral culture, PCR, or HSV-2 seroconversion. An intent-to-treat analysis was conducted.

The secondary endpoints in susceptible partners were:

- time to clinical symptoms of genital HSV-2 in susceptible partners,
- the proportion with HSV-2 seroconversion,
- time to HSV-2 seroconversion,
- the proportion with acquisition of genital HSV-2 (any PCR, culture or serologic diagnosis)
- time to overall acquisition of genital HSV-2,
- the proportion with asymptomatic HSV-2 seroconversion
- time to HSV-2 seroconversion,

The secondary endpoints in the source partners were:

- time to first genital HSV-2 recurrence
- time to first oral HSV-2 outbreak in source partners.

A viral shedding substudy of source patients was conducted at 4 U.S. sites to assess the efficacy of study treatments in the suppression of asymptomatic shedding over a 2-month period. Participants in the study received instructions on daily home viral sample collection, and daily self-examination of genitals. In addition, participants were required to visit the clinic biweekly to provide a history of HSV-2 symptoms and recurrences since the last visit, to undergo a genital exam and viral sample collection, and to return collections of daily home viral samples.

### **Results: Efficacy**

Fourteen hundred ninety eight couples enrolled in HSV2AB3009; 1484 couples were included in an intent-to-treat (ITT) analysis. Two-thirds of the source partners were female, 90% white, mean age 36.1 years; two-thirds of susceptible partners were male, 90% white, mean age 36.3 years.

The following table lists the rates of HSV-2 infection among susceptible partners by the primary and selected secondary endpoints. Overall HSV-2 acquisition includes subjects with symptomatic HSV-2 acquisition documented by culture, PCR, and/or HSV-2 serology and those with asymptomatic acquisition documented by HSV-2 seroconversion during the study.

**Table 1. Proportion of susceptible partners who acquired HSV-2 infection defined by the primary and selected secondary endpoints**

	<b>Valacyclovir (n=743)</b>	<b>Placebo (n=741)</b>	<b>p-value Odds Ratio (95%CI)</b>
<b>Symptomatic HSV-2 acquisition (Primary endpoint)</b>	4 (0.5%)	16 (2.2%)	0.007 0.25 (0.08, 0.74)
<b>HSV-2 seroconversion</b>	12 (1.6%)	24 (3.2%)	0.04 0.49 (0.24, 0.98)
<b>Overall HSV-2 acquisition</b>	14 (1.9%)	27 (3.6%)	0.038 0.50 (0.26, 0.97)

Time to clinical symptoms was shorter in the placebo group (Kaplan-Meier plots). More female susceptible partners (2.5%, 12/488) acquired clinical genital HSV-2 infection than male susceptible partners (0.8%, 8/996). “Nearly always” (90-100%) condom use was reported for vaginal and anal sex by 200/741 (30%) in the placebo group and 223/743 (30%) in the valacyclovir group. Most couples did not use condoms for oral sex.

Greater than 20% of the subjects discontinued treatment prematurely. The primary reasons for dropping out include withdrawal of consent, loss to follow-up, and the ending of relationships. The percentage of dropouts was much higher than the percentage of patients classified as having clinical evidence of a first episode of genital HSV-2. The results of the primary analysis may not be robust in the presence of such a high proportion of dropouts.

#### **Viral HSV-2 Shedding Sub-Study**

Eighty-nine source patients enrolled in the two-month study of HSV-2 shedding (39 valacyclovir and 50 placebo patients). Forty-one of 50 (82%) of the placebo patients shed HSV-2 on at least one day during the substudy compared to 19/39 (49%) in the valacyclovir-treated patients (p=0.002). The mean percentage of days on which subjects shed virus when lesions were not present (asymptomatic shedding) was 7.8% in the placebo group and 2.8% in the valacyclovir group (p<0.001).

#### **Results: Safety**

In the current labeling of valacyclovir, the Warnings section includes the following: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease and also in allogeneic bone marrow transplant and renal transplant recipients participating in clinical trials of valacyclovir at doses of 8 grams per day. There were no reports of thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) in this study.

No deaths were reported. Twelve placebo and 14 valacyclovir-treated patients experienced serious adverse events. Five placebo and 12 valacyclovir source partners experienced an adverse event leading to discontinuation during double-blind therapy. Headache was the most common adverse event leading to discontinuation of study drugs.

**Table 2. Frequently reported adverse events among source partners**

<b>Adverse event</b>	<b>Valacyclovir (N=743)</b>	<b>Placebo (N=741)</b>
<b>Any event</b>	588 (79%)	553 (75%)
<b>Headache</b>	215 (29)	192 (26)
<b>Nasopharyngitis</b>	122 (16)	110 (15)
<b>URI</b>	69 (9)	75 (10)
<b>Pharyngo-laryngeal pain</b>	61 (8)	55 (7)
<b>Diarrhea</b>	62 (8)	50 (7)
<b>Influenza</b>	60 (8)	51 (7)
<b>Back pain</b>	62 (8)	44 (6)
<b>Nausea</b>	59 (8)	48 (6)
<b>Sinusitis</b>	56 (8)	34 (5)
<b>Upper abdominal pain</b>	38 (5)	35 (5)

Sixteen pregnancies occurred during the study: 8 in the valacyclovir group, 8 in the placebo group. Five pregnant subjects received valacyclovir for suspected HSV-2, four source patients and one susceptible partner. Two healthy children and two spontaneous abortions occurred among the four pregnant valacyclovir-treated source patients; the valacyclovir-treated pregnant susceptible partner elected abortion. Of the seven pregnant source partners in the placebo group, 3 delivered healthy children, 3 spontaneous and one elective abortion occurred.

#### **Summary of Issues - Questions**

Several issues are raised by examination of the data in this sNDA. The population in the study may vary from those treated in a typical practice setting in a number of ways: e.g., the study setting offered enhanced treatment of source patients with herpes recurrences and of susceptible partners with initial symptomatic episodes, but excluded non-monogamous couples, same-sex couples, and the presence of other STDs, including HIV. It is likely that patients will be treated for longer than 8 months. Therapeutic compliance may diminish when asymptomatic HSV-2-infected persons receive treatment for protecting partners, with no immediate personal benefit. The extent to which some infected persons might be less cautious about using condoms and avoiding sex when herpes outbreaks occur may blunt the public health impact of chemotherapy. In addition, more widespread use and off-label use, including transient use, of valacyclovir may lead to the development of drug resistance.

We appreciate your attention to these issues, and any others you wish to raise, as you consider the following questions:

1. Does the information presented by the applicant support the use of valacyclovir to reduce the risk of transmission of genital herpes among monogamous, heterosexual couples?
  - a. If the answer is yes, please address questions 2-5.
  - b. If the answer is no, what additional studies are needed?

2. Does the information presented support the use of valacyclovir to reduce the risk of transmission of genital herpes among populations other than monogamous, heterosexual couples, such as homosexual men, and men and women with multiple partners? What about use among persons who may also be infected with and/or exposed to other sexually transmitted agents? What about use among sexually active individuals who are asymptomatic carriers of HSV-2 infection?
  - a. If the data are supportive for an indication broader than monogamous, heterosexual couples, please specify those populations.
  - b. If the data are not supportive for a broader indication, what studies would you recommend and how would you design such studies?
3. In your opinion, what impact will marketing of valacyclovir for reduction of genital herpes transmission have on use of condoms and abstinence from sex during clinical HSV-2 outbreaks?
4. Although patients in the registrational trial were treated for eight months, valacyclovir for suppression of transmission of genital herpes will likely be used for significantly longer periods of time. What additional studies would you suggest to evaluate the potential for longer-term adverse events, including development of resistance to valacyclovir?
5. The primary endpoint in HS2AB3009 was the proportion of couples with clinical evidence of a first episode of genital HSV-2 in the susceptible partner. Would you recommend that primary endpoint in future studies with agents to prevent transmission of HSV-2? If not, what primary endpoint would you recommend?

## **ATTACHMENTS**

- A. Sexually Transmitted Diseases Treatment Guidelines – 2002, Centers for Disease Control and Prevention, Atlanta, Georgia. Excerpt of pages 1-20.
- B. Wald A, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA 2001; Vol. 285, No.24