CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-487 /S-005

CLINICAL PHARMACOLOGY/ BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20- 487 (SLR 005)
TYPE: Labeling Supplement
DRUG: Valtrex® (Valacyclovir hydrochloride)
INDICATION: Treatment and Suppression of Herpes Infection
APPLICANT: GlaxoSmithKline
OCPB Division: DPEIII
OND Division: Division of Antiviral Drug Products
SUBMISSION DATE: February 19, 2004
REVIEWER: Vikram Arya, Ph.D.
TEAM LEADER: Kellie Reynolds, Pharm.D.

I. Executive Summary

In this supplement, the sponsor seeks to make labeling changes to the **"PRECAUTIONS: Nursing Mothers"** subsection of the package insert. The proposed wording is based on data from the manuscript provided (Sheffield et al, *Am J Obstet Gynecol*, 2002, **186**, 100-102) with the submission.

1.1. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted in this labeling supplement and has concluded that the information provided is adequate to make the proposed labeling revisions with the following minor modification:

"PRECAUTIONS: Nursing Mothers" subsection: After acyclovir dosage of 0.6 mg/kg/day add, "This would result in less than 2 % of the exposure obtained after administration of a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir to the nursing infant.

1.2. Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Valtrex® (valacyclovir hydrochloride) is the hydrochloride salt of the L-valyl ester of the antiviral drug acyclovir (ZOVIRAX® Brand, GlaxoSmithKline). Valtrex is rapidly converted to acyclovir in the liver. The oral bioavailability of valacyclovir is 3-5 times greater than acyclovir in non-pregnant adults. The concentrations of valacyclovir in human breast milk had not been previously investigated. An increase in levels of acyclovir after administration of valacyclovir (due to increased bioavailability) was anticipated.

The sponsor has provided pharmacokinetic data from a previously published article,"Acyclovir concentrations in human breast milk after valaciclovir administration", Sheffield et al, *Am J Obstet Gynecol*, 2002, **186**, 100-102. The study design and the major findings from this article

are discussed in detail in the attached review. Table 1 shows the summary of acyclovir pharmacokinetic parameter estimates in maternal serum and breast milk after single dose administration of valacyclovir.

Table 1. Summary of Acyclovir Pharmacokinetic Parameter Estimates* in Maternal Serum and Breast Milk after Single Dose (500 mg) Valacyclovir Administration.

Parameter	Serum	Breast Milk	Breast Milk to Serum Ratio#
T_{max} (hr)	1.0 (1.0-2.0)	4.0 (2.0-4.0)	2.0 (2.0-4.0)
C_{max} (μg/mL)	2.7 (2.0-3.4)	4.2 (1.1-6.4)	1.4 (0.5-2.3)
AUC(μg*hr/mL)	14.7 (8.7-17.7)	26.9 (20.7-32.8)	2.2 (1.4-2.6)
$t_{1/2}$ (hr)	2.5 (1.6-5.1)	2.1 (1.3-12.2)	1.0 (0.5-2.4)

*: Values denote median and range.
#: Values denote median and range of individual subject ratios.

The major results (as presented in the article) indicate:

- Valacyclovir was undetected in the maternal serum, breast milk, or infant urine at any time point during the study indicating the rapid conversion of valacyclovir to acyclovir.
- The median peak acyclovir concentrations were 44 % greater (1.4 fold higher) and the AUCs were 2.2 fold higher in breast milk compared to the human serum.
- There were no apparent differences in acyclovir elimination half-life, on average, between serum and breast milk.
- The article indicates that following the initial dose, the median breast milk acyclovir concentrations were higher than in serum 1.5 hours after the dose and remained higher at all subsequent time points during the day. However, at steady state, serum concentrations were higher (2.7 *vs* 1.7 μg/mL).
- The article suggests that the median infant urine acyclovir concentration at steady state was 0.74 μg/mL.
- The predicted average infant exposure would be 0.61 mg/kg/day. As therapeutic dosing of neonates is 30 mg/kg/day as intravenous acyclovir, the predicted infant exposure after maternal dosing of 500 mg valacyclovir is approximately 2 % of the standard neonatal daily dose of intravenous acyclovir (for details regarding assumptions and prediction of neonatal exposure, please refer to the attached study review).

1.4 Proposed Package Insert

The final approved wording for the "Precautions: Nursing Mothers" subsection of the package insert is included below.

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

1.5 Study Review

The proposed labeling changes are based on the following article:

Acyclovir concentrations in human breast milk after valcyclovir administration. Jeanne S. Sheffield et al. *Am J Obstet Gynecol*, 2002, 186, 100-102.

STUDY DESIGN

The study analyzed the postpartum valacyclovir and acyclovir concentrations in the maternal serum and breast milk of 5 women who were receiving valacyclovir therapy and in the urine from their newborns.

Valacyclovir therapy (500 mg BID) was initiated for 7 days. The daily dose that was chosen is recommended for suppressive therapy of recurrent genital herpes in adults with a history of frequent recurrences ($\geq$ 10 episodes/yr). Matched maternal serum and breast milk samples were obtained immediately before the initial dose of valacyclovir, at 1, 2, 4, and 8 hours after the initial dose, and at the same time on day 5 of valacyclovir treatment (to determine steady state concentrations) and then 24 hours after the 7-day course of medication is completed. A urine sample was obtained from the infants on day 5 of treatment.

The serum samples were analyzed for valacyclovir and acyclovir concentrations with the use of validated high performance liquid chromatography (HPLC) assay. Concentration-time data for acyclovir in serum or breast milk were analyzed by standard non-compartmental analysis. Peak concentrations (C_{max}) and the times at which these concentrations were achieved were estimated by visual inspection of the concentration *vs* time data. The apparent elimination rate constant (k_{el}) was determined by least square regression analysis of the terminal portion of the natural log concentration-time curve. The area under the concentration time curve from time zero to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-last} + C_{last}/K_{el}$ where AUC_{0-last} is the AUC from time zero to the last measured concentration (calculated by linear trapezoidal summation method) and C_{last} is the last measured concentration.

RESULTS

Table 1 shows the summary of acyclovir pharmacokinetic parameter estimates in maternal serum and breast milk after single dose administration of valacyclovir.

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#: Values denote median and range of individual subject ratios.

The major results of the study were:

- Valacyclovir was undetected in the maternal serum, breast milk, or infant urine at any time point during the study indicating the rapid conversion of valacyclovir to acyclovir.
- The median peak acyclovir concentrations were 44 % greater (1.4 fold higher) and the AUC's were 2.2 fold higher in breast milk compared to the human serum.
- There were no apparent differences in acyclovir elimination half life, on average, between serum and breast milk.
- The article indicates that median breast milk acyclovir concentrations were higher than in serum 1.5 hours after the initial dose and remained higher at all subsequent time points during the day. However, at steady state, serum concentrations were higher (2.7 *vs* 1.7 μg/mL).
- The article states that the median infant urine acyclovir concentration at steady state was 0.74 μg/mL.
- The predicted average infant exposure would be 0.61 mg/kg/day. As therapeutic dosing of neonates is 30 mg/kg/day as intravenous acyclovir, the predicted infant exposure after maternal dosing of 500 mg valacyclovir is approximately 2 % of the standard neonatal daily dose of intravenous acyclovir (for details regarding assumptions and prediction of neonatal exposure, please refer to the attached study review).

Summary of Computations Used to Derive Infant Acyclovir Exposure From Breast Milk (as presented in the Sheffield et.al. article)

- The median AUC_{∞} in the breast milk after the initial valacyclovir dose was 26.9 μg/mL.
- With 500 mg valacyclovir administered every 12 hours, the average steady state median concentration of acyclovir in breast milk would be 2.24 μg/mL.
- Assuming 750 mL of breast milk production and neonatal ingestion per day, an average of 1.68 mg/day of acyclovir would be ingested by a breastfeeding infant.
- With the use of an average infant weight of 2.75 kg, the infant exposure would be approximately 0.61 mg/kg/day (1.68/2.75).
- Since therapeutic dosing for neonates is often 30 mg/kg/day as intravenous acyclovir, the calculated amount of acyclovir that would be ingested by an average neonate after the maternal valacyclovir dosing of 500 mg bid is negligible (approximately 2 % of the standard neonatal daily dose of intravenous acyclovir).
- Systemic exposures would be further reduced to < 0.5 % of the daily intravenous acyclovir dosage, given the expected low oral bioavailability of approximately 20 %.

CONCLUSION

The results of the study support the sponsor's conclusion that administration of Valtrex 500 mg BID to nursing mothers results in less than 2 % of the exposure obtained after a standard neonatal dose of 30 mg/kg/day of intravenous acyclovir) in the nursing infant.

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/s/

Vikram Arya
12/8/04 01:26:59 PM
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This review was originally checked into DFS on Nov 15, 2004. Due to DFS problems, this review was checked in again on December 8, 2004.

Kellie Reynolds
12/9/04 09:20:17 AM
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