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APPLICATION NUMBER:

21-478

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS
TEAM LEADER NOTE

NDA: 21-478
DRUG: Zovirax® (acyclovir) cream, 5%
SPONSOR: GlaxoSmithKline
TYPE: NDA

TEAM LEADER: Kellie Schoolar Reynolds, Pharm.D.
SUBMISSION DATE: March 29, 2002
REVIEW DATE: December 17, 2002

NOTE: This application does not include a Human Pharmacokinetics and Bioavailability Section (Item 6). Acyclovir exposure data are available from one pharmacokinetic study, included in Item 8. A full clinical pharmacology and biopharmaceutics review is not needed.

The applicant previously submitted and withdrew NDA 21-122 for the same product and indication. The application was not withdrawn for safety or efficacy reasons.

BACKGROUND: The following acyclovir formulations are marketed in the U.S.: 5% ointment, 200 mg capsules, 200 mg/5 mL suspension, 400 mg and 800 mg tablets, and acyclovir sodium for injection. The indications for these formulations include treatment of Herpes Simplex, Herpes Genitalis, Herpes Labialis, Varicella-Zoster (shingles), and chickenpox. The highest recommended doses for adults are (oral) 800 mg q4hr, 5 times per day, for 7 to 10 days and (IV) 10 mg/kg q8hr for 7 days.

Acyclovir 5% cream has been available since 1982 and 1991 in numerous countries worldwide as a prescription product and as an OTC product, respectively.

SUMMARY:
Proposed indication: Treatment of recurrent herpes labialis (cold sores) in adults and adolescents 12 years of age and older.

Proposed dosage and administration: Apply 5 times per day for 4 days. Therapy should be initiated as early as possible following onset of signs and symptoms.

How supplied: Acyclovir 5% cream is supplied in 2-gram tubes. Each gram contains 50 mg of acyclovir in an aqueous cream base.

Quantitative Composition:

Ingredient	Quantity %w/w	mg/g
Acyclovir, USP	5.0	50
Propylene Glycol, USP		
White Petrolatum, USP		
Cetostearyl Alcohol, NF		
Mineral Oil, USP		
Poloxamer 407, NF		
Sodium Lauryl Sulfate, NF		
Purified Water, USP		

Clinical trials: The application includes the results from two placebo-controlled pivotal studies (ZOVA 3003 and ZOVA 3004) and two supportive studies (ZOVA 3001 and ZOVA 3002). The proposed commercial formulation was used in these studies.

Pharmacokinetics: [For more details regarding acyclovir pharmacokinetics, see the pharmacokinetics reviews for NDAs 18-603 (IV), 18-604 (ointment), 18-828 (capsules), 19-909 (suspension) and 20-089 (tablets)]

The applicant conducted one study (BLWY/83/0001) to assess the systemic absorption of acyclovir 5% cream when applied to the skin of six normal volunteers. The cream was applied to a 710 cm^2 skin area five times daily for four days, with the total amount applied ranging from 4.2 g to 10.4 g. No occlusive dressings were applied. Plasma concentrations were measured 1 hour after the last application, and urinary excretion was assessed on day 4. The plasma acyclovir concentrations 1 hour after the last application were below the detection limit [redacted] in five subjects, and barely detectable [redacted] in one subject. Mean urinary excretion was 0.058% of the applied dose.

These results indicate that systemic exposure to acyclovir is minimal following application of acyclovir 5% cream. The systemic concentrations are much lower than those following oral administration (Cmax at steady-state following 200 and 800 mg doses are 0.83 µg/mL and 1.61 µg/mL) or IV infusion (Cmax at steady-state following 10 mg/kg q8hr is 22.9 µg/mL). Systemic exposure is negligible with the currently marketed acyclovir 5% ointment. It is noted that systemic exposure may be higher following application to broken skin. However, systemic exposure will not approach that observed with the approved oral and IV formulations.

The proposed ZOVIRAX Cream label indicates the minimal systemic absorption of acyclovir.

Conclusion: There are no outstanding clinical pharmacology or biopharmaceutics issues.

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/s/

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