CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-436

SUMMARY REVIEW

Decisional Memorandum to the File

Date:	July 31, 2009
From:	Jeffrey S. Murray, M.D., M.P.H. Deputy, Division of Antiviral Products
Subject:	Summary and Recommendations
NDA/BLA #:	22-436
Proprietary / Generic (USAN) names	Acyclovir 5% and Hydrocortisone 1% cream
Dosage forms / strength	Topical cream
Proposed Indication(s)	For the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (12 years of age and older)

1. Introduction/Background/Regulatory History

Medivir AB has submitted a 505(b)(2) application for Acyclovir 5% and Hydrocortisone 1% cream (A-H cream). Acyclovir cream 5% (manufactured by GSK) is approved for the treatment of herpes labialis (cold sores). Hydrocortisone cream has many generic versions, and in the 1% strength is available without prescription for the treatment of various minor skin conditions. Hydrocortisone cream products do not have indications for the treatment of herpes labialis. Medivir submitted clinical data to show that both acyclovir and hydrocortisone in this fixed dose topical product (A-H cream) have efficacy in the treatment of herpes labialis. Although both active ingredients in this FDC topical are approved, the combination product has not been previously approved and there is no reference listed drug for this product. Therefore this application falls under 505(b)(2) regulations.

The applicant conducted required dermal irritation studies and clinical efficacy and safety studies to support approval of A-H cream. During development of this product the applicant relied on FDA's previous findings of safety and efficacy from NDA 21-478 (Acyclovir cream) and ANDA 80472 [Hytone (hydrocortisone) cream] to obviate the need for repeating additional nonclinical studies including. FDA agreed certain nonclinical studies, such as standard animal toxicology studies with acyclovir and hydrocortisone did not need to be repeated prior to conducting their clinical efficacy studies or to support approval.

2. CMC

2.1. General Product Quality considerations

Refer to Dr. Jeffrey Medwid's review for details regarding product quality. Dr. Medwid concludes that the applicant "provided sufficient information on raw material controls, manufacturing processes and process controls for assuring consistent product quality of the drug product. The NDA has also provided sufficient stability

information on the drug product to assure strength, purity, and quality during the expiration dating period."

2.2 Facilities Review/Inspection
An overall compliance recommendation was made on July 31, 2009 with an acceptable cGMP status for all facilities involved in the manufacture, packaging, and testing of the drug substance and product.

2.3 Issues Needing Resolution
The approval letter will specify that the carton label list all A-H cream ingredients.

3. Microbiology
Refer to the Micobiology Review prepared by Dr. Nilambar Biswal who found no issues that would preclude the approval of A-H cream. The applicant conducted a study evaluating use of A-H cream in immunocompromised patients and there were no signals to suggest that hydrocortisone would increase the rate of emergence of resistance to acyclovir.

4. Nonclinical Pharmacology/Toxicology
4.1. General Nonclinical Pharmacology/Toxicology Considerations
Refer to the Review prepared by Dr. Anita Bigger who found no issues that would preclude the approval of A-H cream for the proposed indication. Dr. Bigger reviewed a single skin irritation study in animals and found that A-H cream is essentially nonirritating in the animal study. Other animal toxiciology studies were not conducted but relied on FDA's previous findings of safety and efficacy for approval of individual acyclovir and hydrocortisone cream products.

Long-term carcinogencity studies in animals have not been conducted and are not required for the current indication.

5. Clinical Pharmacology/Biopharmaceutics
The product is a topical cream with little to no systemic absorption. The Clinical Pharmacology and Biopharmacuetics review prepared by Dr. Stanley Au concludes that the application is acceptable for approval. The clinical pharmacology review addresses a single topical vasoconstriction trial conducted in healthy subjects. Four other trials conducted in healthy subjects were review by a consultant from the Division of Dermatology and Dental Products. (See Clinical Safety below).

Dr. AU concludes that although the vasoconstriction study was not conducted according to FDA's current recommendations, the effects of hydrocortisone are well characterized. Also the hydrocortisone vasoconstriction effects for A-H cream in the applicant's study were similar to that produced by hydrocortisone itself. Therefore this combination product is considered safe for approval from a clinical pharmacology perspective.

6. Clinical/Statistical

6.1. Efficacy

Please refer to the combined clinical-statistical reviewed prepared by medical officer, Dr. Kirk Chan-Tack, and statistician, Dr. Susan Zhou. Both reviewers conclude that A-H cream is safe and efficacious and that the applicant is sufficient to warrant approval.

The application includes three phase 3 trials. The efficacy and safety data from Study 609-04 support clinical efficacy of safety A-H cream in adults and is considered the most essential study for approval. Study 609-06 provides additional safety data in immunocompromised adults. Study 609-07 evaluated the safety of A-H cream in adolescents. Extrapolation of efficacy for A-H Cream in adolescents is considered reasonable based on the available data since the course of recurrent herpes labialis and the effects of A-H Cream are sufficiently similar in adults and adolescents.

6.1.1. Phase 3/Essential Clinical Study

Study 609-04: a randomized, double-blind, active-controlled, vehicle-controlled, subject initiated trial comparing efficacy and safety of A-H cream versus acyclovir cream versus placebo (vehicle) for treatment of recurrent herpes simplex labialis

Immunocompetent adults, ages 18 years or older, who had a history of recurrent herpes labialis with at least three episodes during the last 12 months were eligible for the study. Subjects were randomized to A-H Cream (minimum of 535 evaluable subjects), acyclovir in A-H Cream vehicle (minimum of 535 evaluable subjects), or A-H Cream vehicle (minimum of 200 evaluable subjects). Study medications were administered five times daily for five days. Treatment was started within one hour of experiencing signs or symptoms of a herpes recurrence (prodromal symptoms or erythema), and prior to the first clinical sign of a cold sore (no swelling, blister or later stage lesion). Subjects were seen at the study clinic within 18 hours of treatment initiation and were followed daily at the clinic throughout the five-day treatment period and daily until loss of hard crust. Subjects recorded lesion stage, tenderness, and concomitant medications twice daily in a diary.

The trial was designed to show superiority of A-H Cream compared to acyclovir and vehicle for the primary endpoint, the proportion of subjects with non-ulcerative herpes recurrences. These comparisons are made in order to show the contribution of hydrocortisone and to show the overall effect is not due to the vehicle. Also, the study was designed to show superiority of A-H Cream compared to vehicle for the secondary endpoint, episode duration. This comparison was made to show hydrocortisone does not adversely affect acyclovir antiviral efficacy.

Overall, 42.6% of subjects in the A-H Cream arm, 35.6% of subjects in the acyclovir (5% acyclovir cream + vehicle) arm and 25.4% of subjects in the

vehicle (placebo) arm had non-ulcerative HSV recurrences. Thus, A-H Cream was numerically superior to vehicle ($p<0.001$), and superior to acyclovir ($p<0.05$), for the reduction of ulcerative herpes lesions. The median episode durations were 4.77 days in the A-H Cream and 5.09 days in the vehicle arm, respectively. The reduction in median episode duration (A-H Cream - vehicle) using the Hodges-Lehmann's (H-L) approach was 0.38 days ($p>0.05$). Furthermore, subjects who were treated with A-H Cream had a significant reduction in median duration to normal skin of 7 days, an approximate one day reduction compared to more than 8 days in the vehicle arm ($p <0.001$).

The primary study analysis was pre-defined to show that A-H cream was superior to acyclovir alone with a p-value of 0.001, since efficacy relied on one study, and one needed to show a robust contribution of hydrocortisone in the treatment of herpes labialis. Although the A-H cream comparison with acyclovir was not significant at the 0.001 level, it was convincingly numerically superior and multiple secondary and tertiary endpoints showed that A-H cream was efficacious and that each component appeared to provide a contribution.

6.1.2. Other efficacy studies

Study 609-06: a randomized, double-blind, active controlled, subject initiated trial comparing A-H Cream to acyclovir cream for treatment of recurrent herpes simplex labialis in immunocompromised patients

This was a phase 3 multi-center, randomized, double-blind, active-controlled, trial to evaluate the safety and efficacy of A-H Cream versus acyclovir in A-H Cream vehicle for the treatment of recurrent herpes labialis in immunocompromised patients. HIV+ adults with stable infection (CD4 100-500 cells/mm^3), ages 18 years or older, who had a history of recurrent herpes labialis with at least two episodes during the last 12 months were eligible for the study. Other inclusion/exclusion criteria were similar to Study 609-04. A total of 230 subjects were randomized in a 2:1 ratio (A-H Cream:acyclovir), of which 80 were predicted to have evaluable data. Study medications were administered five times daily for five days. Treatment was started at the first signs or symptoms of a herpes recurrence. The primary endpoint was episode duration and the secondary endpoint was time to next herpes recurrence.

The trial showed that hydrocortisone did not impair the healing time of acyclovir in immunocompromised hosts (primarily HIV positive patients), and in fact the number of ulcerative recurrences was numerically lower for A-H cream compared to acyclovir, which is supportive of a positive contribution of hydrocortisone in the treatment of herpes labialis.

6.1.3. Issues needing resolution

There are no issues remaining to be resolved.

6.2. Safety

The Division has not identified any significant safety issues A-H cream. Adverse reactions included: drying or flaking of the skin; transient burning or tingling, erythema; pigmentation changes. Most adverse reactions were mild in nature.

The Division of Dermatology and Dental Products reviewed the following four studies:

- 21 Day Cumulative Irritation Patch Test
- Human Repeat Insult Patch Test
- Phototoxicity Study
- Photoallergy Study

They concluded that A-H cream has high irritation potential and may be sensitizing. It appears that the hydrocortisone and/or vehicle components, and not the acyclovir, are responsible for sensitization. Studies of A-H cream revealed no phototoxic or photoallergic potential.

7. Risk Minimization Plan

Given the safety profile for the product, no risk minimization plan is recommended at this time.

8. Summary of Regulatory Issues

There are no regulatory issues, including those that relate to 505(b)(2) applications, that preclude approval of the application

9. Advisory Committee Meeting

This NDA/product was not taken to an Advisory Committee

10. Proprietary Name/Carton and Container Labels

The applicant proposed the proprietary name Lipsovir, which DMEPA (Division of Medication Error Prevention and Analysis) deemed unacceptable because it contains the United States Adopted Name (USAN) stem 'vir." This stem is considered reserved for standard names only and is not recommended for use in proprietary names. The use of stems in proprietary names can result in multiple proprietary names that are similar to each other and USAN names, thus increasing the chance of confusion among products.

11. DSI Audits

Clinical Inspections were acceptable. Inspectors did not uncover data integrity issues

12. Conclusions and Recommendations

12.1. Regulatory Action

I concur with all of the reviewers of the review team that A-H cream should be approved for the treatment of recurrent herpes labilalis (cold sores)

12.2. Postmarketing Studies

The sponsor is required to conduct one postmarketing study under PREA.

> Deferred pediatric study under PREA for the treatment of recurrent herpes labialis in pediatric patients ages greater than 6 years to less than 12 years.
> Final Report Submission: May 1, 2013

We are waiving the pediatric study requirement for ages less than 6 years of age because necessary studies are highly impracticable and the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. This is because of the pathophysiology and epidemiology of the disease. Herpes labialis in children less than 6 years of age is generally a primary infection, and not a recurrence.

This is a representation of an electronic record that was signed 'ectronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY S MURRAY
07/31/2009