

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-436

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY MEMORANDUM

NDA: 22-436	Submission Date: September 30, 2008
Brand Name	To be determined (original brand name was not accepted by the Office of Surveillance and Epidemiology)
Generic Name	acyclovir, hydrocortisone
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Sponsor	Medivir AB
Formulation; strength(s)	acyclovir 5%, hydrocortisone 1% (combined topical cream)
Indication	Treatment of recurrent herpes labialis (cold sores)
Review Type	505(b)(2) NDA

A) Introduction

This memorandum documents the clinical pharmacology review for NDA 22-436, a 505(b)(2) application for a cream containing a combination of two marketed products, acyclovir and hydrocortisone. The indication proposed by the sponsor is for the early treatment of the signs and symptoms of recurrent herpes labialis (cold sores) with the objective of preventing and decreasing the duration of ulcerative cold sores in adults and adolescents. In the draft labeling changes sent to the sponsor, the indication was modified by the clinical reviewer to early treatment of recurrent herpes labialis (cold sores) with the objective of decreasing the likelihood of ulcerative cold sore occurrence in adults and adolescents.

The sponsor (Medivir) did not conduct human pharmacokinetic trials in support of the NDA. During the preNDA meeting, the Food and Drug Administration agreed that pharmacokinetic trials were not needed for the acyclovir and hydrocortisone combination product.

The clinical pharmacology review addresses a vasoconstriction trial conducted in healthy subjects. Four other trials conducted in healthy subjects for the combination product were reviewed by the Division of Dermatology and Dental Products: a) a 21 day cumulative irritation patch test to evaluate skin irritation, b) a human repeat insult patch test to evaluate skin sensitization, and two trials that evaluated the product's phototoxicity and photoallergy potential.

B) Trial information

The clinical pharmacology review evaluates a vasoconstriction (skin blanching) trial (Medivir trial number 98-609-001: Topical activity of formulations with a glucocorticosteroid using vasoconstriction [skin blanching]), which the sponsor conducted to evaluate the pharmacologic glucocorticosteroid effects of a marketed topical hydrocortisone formulation compared to two different topical Medivir formulations consisting of acyclovir (5%) and hydrocortisone (1%). The purpose of this trial was to determine which Medivir formulation demonstrated hydrocortisone vasoconstriction effects most similar (or greater) to hydrocortisone by itself.

The two topical Medivir formulations differed only in the percentage of isopropylmyristate ~~_____~~, with one formulation containing _____ (labeled as ME-609) and the other formulation containing _____ (labeled as ME-609B). In response to follow up questions, according to the sponsor, the ME-609B formulation theoretically is expected to result in a greater degree of skin blanching since the formulation has a higher percentage of isopropylmyristate.

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In this trial, during Day 1, the subjects applied the two Medivir experimental acyclovir (5%) and hydrocortisone (1%) cream formulations and commercially available hydrocortisone 1% cream three times a day. The commercially available hydrocortisone 1% cream was manufactured in Sweden by CCS AB. On Days 2 to 7, the subjects applied the three creams five times a day. For all three creams, both the extent of skin blanching and measurement of blood flow using laser doppler technology were used in evaluating vasoconstriction. On Day 1, this was determined one hour after each application. On Days 2 to 7, this was evaluated once daily one hour after the first application.

The subjects also applied acyclovir (Zovirax®) 5% cream on Days 1 to 7 at the same dosing frequencies as the acyclovir/hydrocortisone or hydrocortisone creams. The sponsor obtained acyclovir cream from Warner-Lambert Consumer Healthcare, UK.

The trial was double blinded for the acyclovir/hydrocortisone or hydrocortisone creams and open label for acyclovir 5% cream.

The trial design is displayed in Table 1 below.

Table 1-Trial 98-609-001 design

Day -14 to 0	Day 1 (0-24 h)		Day 2 - 7
	Treatment 3 times daily with all three-study treatments. Discharge of subjects after 24 hours.		Treatment 5 times daily with one of the study treatments.
<i>Screening</i> -Demographic data -Medical history	<i>Pre-treatment baseline</i> (just prior to each study drug application): - Blood flow - Signs of atrophy	<i>One hour after each application</i> of study drug: - Skin blanching - Blood flow	<i>Daily visits to the hospital.</i> One hour after first application of the day: - Skin blanching - Blood flow - Signs of atrophy (Baseline values are obtained from an area adjacent to the treatment area)
	←Treatment with acyclovir 5% cream for safety evaluation→		
	Day 1 (0-24 h): 3 times daily		Day 2-7: 5 times daily
← RECORDING OF ADVERSE EVENTS DURING ENTIRE STUDY PERIOD →			

Skin blanching was evaluated on a scale from 0 to 3:

0 = normal skin

0.5 = very faint blanching

1 = faint blanching

2 = clear blanching

3 = intense blanching

A grading of 0.5 between two grades was accepted.

In response to follow up questions, the skin blanching assessments were performed by a nurse, who was trained by the principal investigator. In the trial report, the principal investigator was affiliated with the Department of Oto-Rhino-Laryngology at the trial site.

C) Results

The reported median hydrocortisone vasoconstriction scores for all days (Days 1 through 7) were zero, which is the expected result for a glucocorticosteroid with low potency antiinflammatory effects.¹

The skin blanching results indicate that the hydrocortisone vasoconstriction effects of the two hydrocortisone/acyclovir formulations were similar both to each other and to hydrocortisone by itself when comparing median skin blanching effects. However, a greater range of skin blanching scores was observed for the ME-609B formulation compared to the ME-609 formulation for the first 24 hours or Day 1 (Figures 1A and 1B). On Days 2 to 7, minimal differences were observed for the two formulations, with 0.5 reported as the maximum skin blanching score (Figure 2). Therefore, the sponsor selected the ME-609 formulation for clinical development since the hydrocortisone effects were the most similar to hydrocortisone by itself.

Figure 1A-Skin blanching (Day 1)

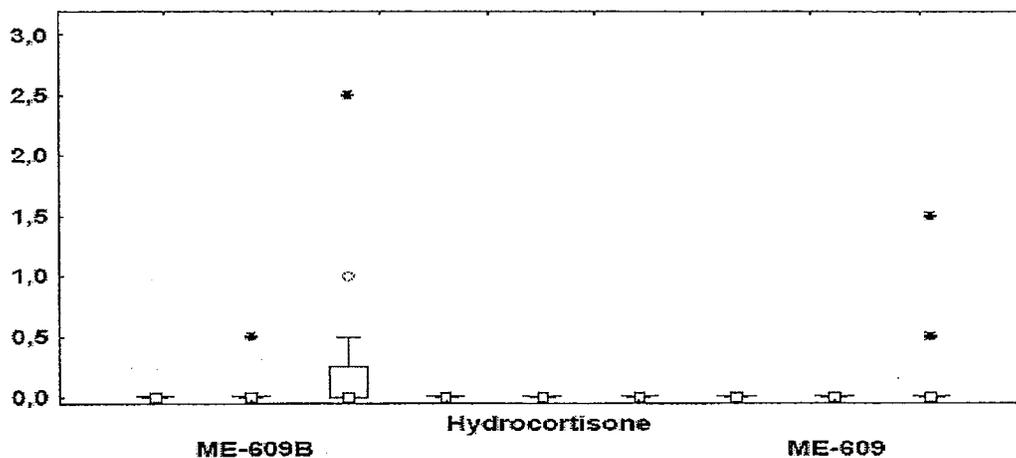


Figure 1B-Maximum skin blanching (Day 1)

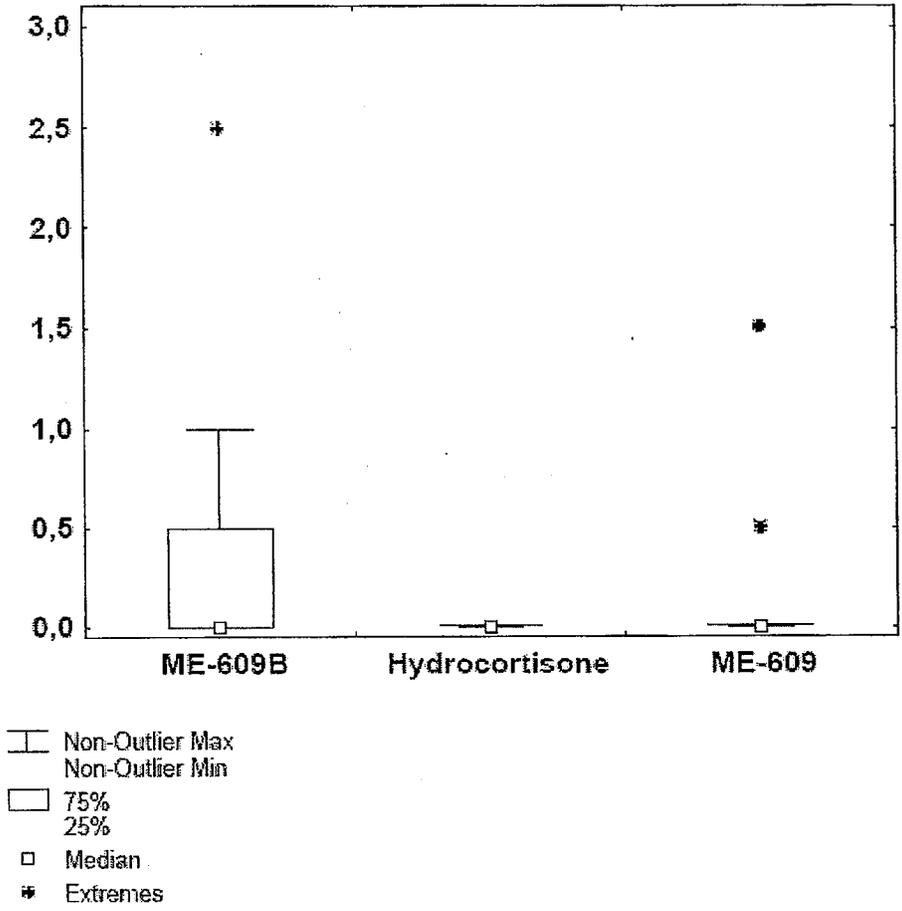
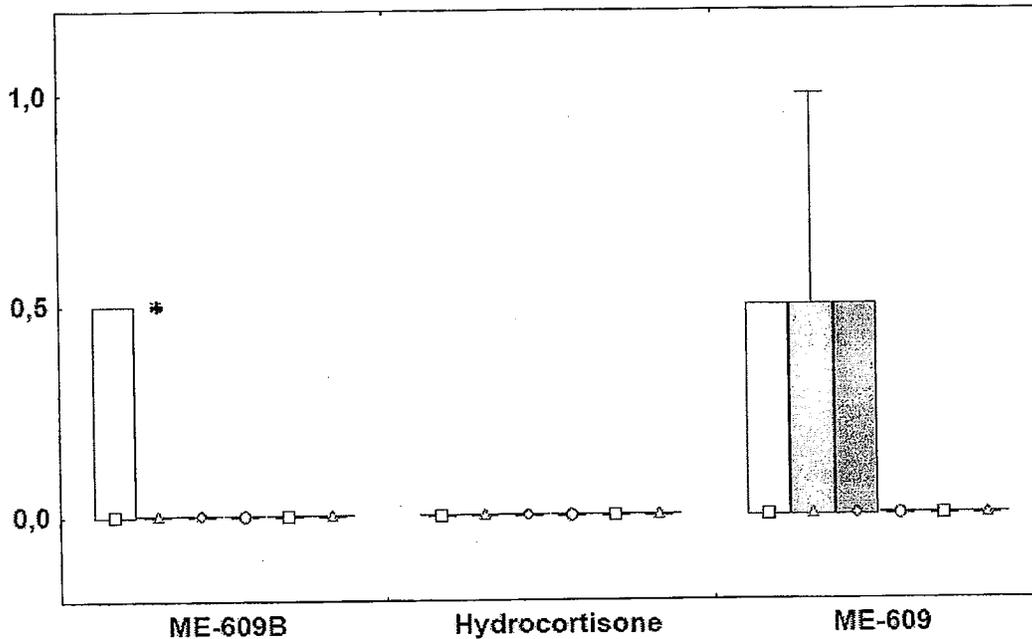


Figure 2-Skin blanching (Days 2 to 7)



There were outlier vasoconstriction scores noted for both Medivir formulations during Day 1 in which discernable vasoconstrictive effects were observed. The cause for these outliers is unclear. In response to follow up questions, Medivir indicated that no potential causes could be determined for the outlier values, including protocol violations. The subjects with outlier values experienced typical adverse events associated with topical medications (redness and dry skin).

OCP did not review the laser doppler results. These results were not reviewed since the validity of using laser doppler results to evaluate skin blanching has not been established.

The most common adverse events were topical redness and dryness for the two Medivir acyclovir/hydrocortisone formulations. No adverse events were reported for hydrocortisone. Topical redness and dryness adverse events were more frequent for the acyclovir 5% cream compared to the two Medivir formulations.

D) Discussion

The trial was not conducted according to the FDA's Division of Dermatology and Dental Product's current recommendations for a vasoconstriction (skin blanching) trial and therefore was not considered acceptable by the dermatology clinical pharmacology review team.

The current recommended design includes the use of six arms as listed below:

- 1) Control (no treatment applied)
- 2) Vehicle only
- 3) Test product
- 4) Low potency glucocorticosteroid

- 5) Medium potency glucocorticosteroid
- 6) High potency glucocorticosteroid

However, the impact of not conducting the trial according to current recommendations on the sponsor's application is minimal since the vasoconstriction effects of hydrocortisone are well characterized and the hydrocortisone vasoconstriction effects for the two Medivir acyclovir/hydrocortisone formulations were similar to hydrocortisone by itself.

E) Labeling Recommendations

OCP reviewed the relevant clinical pharmacology portions of the sponsor's proposed prescribing information (label). The reviewer examined the FDA approved labels for existing hydrocortisone topical products and requested feedback from the dermatology clinical pharmacology team leader. Subsequently, DAVP sent recommended changes to the sponsor to revise the label to include language consistent with existing hydrocortisone topical products for describing the pharmacokinetics of hydrocortisone. The proposed labeling information in regards to the pharmacokinetics of acyclovir was acceptable. The proposed revised labeling is displayed in Table 2 below.

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F) Conclusions

The trial was not considered acceptable by the dermatology clinical pharmacology review team since it was not conducted according to the FDA's Division of Dermatology and Dental Product's current recommendations for a vasoconstriction (skin blanching) trial. However, the vasoconstriction effects of hydrocortisone are well characterized and the hydrocortisone vasoconstriction effects for the two Medivir acyclovir/hydrocortisone formulations were similar to hydrocortisone by itself. Therefore, the vasoconstriction trial design deficiencies do not preclude the 505(b)(2) application for a cream containing a combination of two marketed products, acyclovir and hydrocortisone, from being approved.

References

1) Schimmer BP, Parker KL. Chapter 59: Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. Goodman & Gilman's The Pharmacological Basis of Therapeutics - 11th Ed. (2006)

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/s/

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