CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-436

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-436**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**09/30/08**
PRODUCT:	ME-609 (acyclovir, 5% and hydrocortisone, 1%) Cream
INTENDED CLINICAL POPULATION:	**Treatment of recurrent herpes labialis in adults and adolescents.**
SPONSOR:	**Medivir**
DOCUMENTS REVIEWED:	**EDR**
REVIEW DIVISION:	**Division of Antiviral Products**
PHARM/TOX REVIEWER:	**Anita Bigger, PhD**
PHARM/TOX SUPERVISOR:	**Hanan Ghantous, PhD, DABT**
DIVISION DIRECTOR:	**Debra Birnkrant, MD**
PROJECT MANAGER:	**David Araojo, PharmD**

Date of review submission to Division File System (DFS): 6/24/09

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval is recommended.

B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling: None.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: ME609 was found to be non-irritating in a local tolerance study. All other nonclinical findings were reviewed under NDA 21-478 (acyclovir) and NDA 80-472 (hydrocortisone). ME609 is considered safe for topical use.

B. Pharmacologic activity: The pharmacologic activity is reviewed under NDA 21-478 (acyclovir) and NDA 80-472 (hydrocortisone).

C. Nonclinical safety issues relevant to clinical use: None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

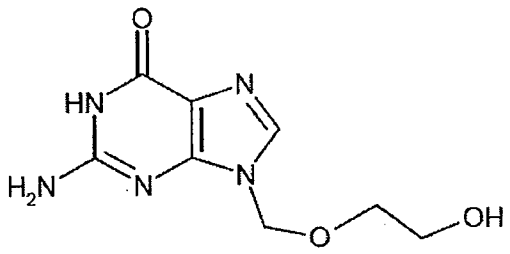
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 42-436
Sequence number/date/type of submission: 000/9-30-08/original
Information to sponsor: Yes ( ) No ( )
Sponsor and/or agent: Medivir AB, P.O. Box 1086, SE-141 22 Huddinge, Sweden

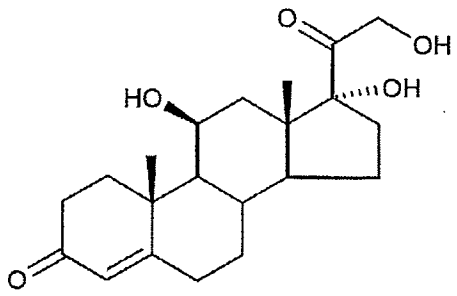
Reviewer name: Anita Bigger, PhD
Division name: Division of Antiviral Products
HFD #: 530
Review completion date: 6/24/09

Drug:

Trade name: Unknown for combination; Zovirax (acyclovir); Hytone (hydrocortisone).
Generic name: None
Code name: ME-609
Chemical name: acyclovir (5%) and hydrocortisone (1%)
CAS registry number: Acyclovir: 59277-89-3; Hydrocortisone: 50-23-7
Molecular formula/molecular weight: Acyclovir: $C_8H_{11}N_5O_3$/225.20; Hydrocortisone: $C_{21}H_{30}O_5$/362.46
Structure:



Acyclovir



Hydrocortisone

Relevant INDs/NDAs/DMFs: IND 58,500/ NDA 21-478, NDA 80-472/ DMF [redacted] b(4)
DMF[redacted]

Drug class: Antiviral and anti-inflammatory.

Intended clinical population: Treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

Clinical formulation: Sponsor table follows.

Table 2.3.P-1: Composition of ME-609 (acyclovir, 5% and hydrocortisone, 1%) Cream[a]

Name of Ingredients	Quantity [% (w/w)]	Function	Reference
Acyclovir	5.0	Active substance	USP
Hydrocortisone	1.0	Active substance	USP
Mineral Oil	[redacted]	[redacted]	USP
White Petrolatum			SP
Isopropyl Myristate			F
Sodium Lauryl Sulfate			F
Cetostearyl Alcohol			NF
Poloxamer 188			NF
Propylene Glycol			USP
Citric Acid,			USP
Sodium Hydroxide	q.s. for pH adjustment	pH Adjustment	NF
Hydrochloric Acid	q.s. for pH adjustment	pH Adjustment	NF
Water			USP

b(4)

b(4)

[a] [redacted] (w/w)

Note: Two excipients, isopropyl myristate (IPM) and Poloxamer 188, are present at levels greater than the IID listed maximum levels for topical cream formulations. Medivir conducted a literature review on these excipients and consulted with DAVP and the Office of Generic Drugs (OGD). DAVP and OGD agreed that the information supplied was sufficient to support the proposed levels of IPM and Poloxamer 188.

Route of administration: Topical.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-436 are owned by GlaxoSmithKline (acyclovir) and Sanofi Aventis (hydrocortisone) or are data for which Medivir has obtained a written right of reference. Any information or data necessary for approval of NDA 22-436 that Medivir does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Medivir does not own (or from FDA reviews or summaries of a

previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-436.

Studies reviewed within this submission: ME609 Primary Skin Irritation Test in Rabbits

All other nonclinical pharmacology and toxicology studies relating to this NDA were reviewed previously under NDA 21-478 (acyclovir, Zovirax) and NDA 80-472 (hydrocortisone, Hytone).

2.6.2 PHARMACOLOGY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.6 TOXICOLOGY

2.6.6.7 Local tolerance

Study title: ME609 Primary Skin Irritation Test in Rabbits

Key study findings: The acute dermal irritation potential of ME609 Cream was investigated in female rabbits. Six rabbits were subjected to a 24-hour exposure to ME609 Cream, applied onto intact and abraded skin on the dorsal trunk, under semi-occlusive patches. The test sites were examined one hour and 48 hours and 11 days after patch removal. No edema and only very slight erythema were observed. Erythema lasted from one hour after patch removal up to five days and in one animal up to Day 9. The primary irritation index on both intact and abraded skin was less than one. ME609 was considered essentially non-irritating.

Study no.: 17130
Volume #, and page #: M4
Conducting laboratory and location: [redacted] b(4)
Date of study initiation: 3-11-99
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: ME609, Batch No. 10582, purity adequate by acceptance criteria
Formulation/vehicle:

Table 2.3.P-1: Composition of ME-609 (acyclovir, 5% and hydrocortisone, 1%) Cream[a]

Name of Ingredients	Quantity [% (w/w)]	Function	Reference
Acyclovir	5.0	Active substance	USP
Hydrocortisone	1.0	Active substance	USP
Mineral Oil			USP
White Petrolatum			USP
Isopropyl Myristate			NF
Sodium Lauryl Sulfate			NF
Cetostearyl Alcohol			NF
Poloxamer 188			NF
Propylene Glycol			USP
Citric Acid.			USP
Sodium Hydroxide	q.s. for pH adjustment	pH Adjustment	NF
Hydrochloric Acid	q.s. for pH adjustment	pH Adjustment	NF
Water.			USP

b(4)

b(4)

b(4)

b(4)

Methods

Doses: 0.5 ml.

Study design: On the day before the test, the hair was clipped from an area (10 cm x 10 cm) across the dorsal trunk of each rabbit. On the next day, the left dorsal trunk was abraded with an abrader in a uniform manner on each rabbit, such that the abrasions penetrated the stratum corneum but did not cause bleeding. Each rabbit was then treated with test material applied topically, under gauze patches (2.5 cm x 2.5 cm) as follows (sponsor's table);

Group	Treatment (ml)	Site	Animal
1	0.5	Left Dorsal Trunk (abraded) Right Dorsal Trunk (non-abraded)	1-6

Each patch was then covered with semi-occlusive tape and elastic bandage was wrapped around the torso of the rabbit to secure the patches.

After 24 hours, the patch was removed and the skin wiped with sterile water. Each test site was evaluated.

Results: No edema and only very slight erythema was observed on non-abraded and abraded sites. Full recovery was observed in all animals by Day 12.

The sponsor's table follows:

ME609
Primary Skin Irritation Test in Rabbits
Table 1 Reaction Scores

Intact site

Animal	Time after Patch Removal or Day of Study/Reaction Score											
	Erythema						Oedema					
	1 h	48 h	Day 5	Day 7	Day 9	Day 12	1 h	48 h	Day 5	Day 7	Day 9	Day 12
1	1	1	1	0	-	-	0	0	0	0	-	-
2	1	1	1	0	-	-	0	0	0	0	-	-
3	1	1	0	-	-	-	0	0	0	-	-	-
4	1	1	1	1	1	0	0	0	0	0	0	0
5	1	1	0	-	-	-	0	0	0	-	-	-
6	0	0	-	-	-	-	0	0	-	-	-	-

Abraded site

Animal	Time after Patch Removal or Day of Study/Reaction Score											
	Erythema						Oedema					
	1 h	48 h	Day 5	Day 7	Day 9	Day 12	1 h	48 h	Day 5	Day 7	Day 9	Day 12
1	1	1	1	0	-	-	0	0	0	0	-	-
2	1	1	1	0	-	-	0	0	0	0	-	-
3	1	1	0	-	-	-	0	0	0	-	-	-
4	1	1	1	1	1	0	0	0	0	0	0	0
5	1	1	1	1	0	-	0	0	0	0	0	-
6	0	1	1	0	-	-	0	0	0	0	-	-

- = Observations complete
h = hours
Scoring system is detailed in Appendix 4

Under the conditions of the study, the primary irritation index of ME609 on intact and abraded rabbit skin is less than one and ME609 is considered to be essentially non-irritating.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: ME609 is considered safe based on the one toxicology study submitted with this NDA and the reviews of NDA 21-478 (acyclovir) and NDA 80-472 (hydrocortisone).

Unresolved toxicology issues (if any): None.

Recommendations: Approval of NDA 22-436.

Suggested labeling: Labeling suggested by the sponsor for nonclinical toxicology is appropriate. All nonclinical toxicology sections refer to the labels for NDA 21-478 (acyclovir) and NDA 80-472 (hydrocortisone). The amount of either drug absorbed from the topical application of ME609 is minimal.

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/s/

Anita Bigger
6/24/2009 04:21:04 PM
PHARMACOLOGIST

Hanan Ghantous
6/25/2009 08:17:50 AM
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