CENTER FOR DRUG EVALUATION AND RESEARCH

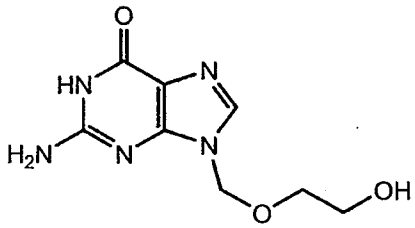
APPLICATION NUMBER:

22-436

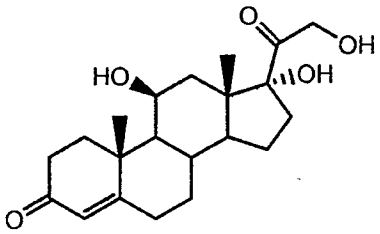
CHEMISTRY REVIEW(S)

NDA 22-436

(acyclovir and hydrocortisone cream, 5%/1%)



Acyclovir



Hydrocortisone

Submitted by:
B&H Consulting Services, Inc
US Agent for Medivir AB

Jeffrey B. Medwid, PhD
ONDQA
Division of Pre-Marketing Assessment II
Branch IV

Note: This is the second review for this NDA. All of the original data provided in the first review is also provided in this review.

Table of Contents

b(4)

b(4)

Chemistry Review Data Sheet

1. NDA 22-436

2. REVIEW #: 2 Note: This is the second review for this NDA. All of the original data provided in the first review is also provided in this review.

3. REVIEW DATE: 31 July 2009

4. REVIEWER: Jeffrey B. Medwid, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Type B Pre-NDA Meeting Briefing Package	23 April 2008
Type B Pre-NDA Meeting Briefing Package	10 October 2007

6. SUBMISSION(S) BEING REVIEWED:

Note: This application was submitted September 30, 2008. The PDUFA goal is August 1, 2008. It is in the e-CTD format.

Submission(s) Reviewed	Document Date	e-CTD Sequence
Original NDA 22-436	30-SEP 2008	0000
Amendment (Request for Trade Name Review - Lipsovir Draft labeling	28-Oct-2008	0001
Amendment (Addendum to Study No. 609-06: 12-Month Follow-up Data)	30-Oct-2008	0002
Amendment (Updated User fee Cover Sheet) All fees paid	19-Nov-2008	0003
Amendment (Updated Form FDA 356h Original Application)	05-Dec-2008	0004
Amendment (Response to Filing Communication from Agency on 4-Dec-2008) updated draft package insert	23-Dec-2008	0005
Amendment (Response to FDA Clinical Comment) to Submit a pediatric study in children 6-11 years old	16-April-2009	0006
Amendment (Response to FDA Clinical Site Investigation comments (Received 19 March 2009)	17-April-2009	0007
Amendment (Pediatric Study Plan)	20-April-2009	0008
Amendment (Updated Pediatric Study Plan)	23-April-2009	0009
Amendment (Response to Clinical Pharmacology Comments)	30-April-2009	0010
Amendment (Response to Statistical Comment)	8-May-2009	0011
Amendment (Final Clinical Study Report No. 609-06)	2-June-2009	0012
Amendment (Draft Labeling)	29-June-2009	0013
Amendment (Response to Labeling comments from Microbiology)	20-July 2009	0014

7. NAME & ADDRESS OF APPLICANT & US AGENT:

Name:	Medivir AB /designates B&H Consulting Services, Inc to represent Medivir AB as US Agent
Address:	PO Box 1086 SE-141 22 Huddinge Sweden
Representative(s):	Annelie Skagerlind, M.Sc.Pharm; Director of Regulatory Affairs
Telephone:	+46 8 5468 3184
Fax	+46 8 5468 3199
e-Mail	annelie.skagerlind@medivir.se

Name:	B&H Consulting Services, Inc
Address:	55 North Gaston Avenue Somerville, NJ 08876
Representative(s):	Elizabeth N. Dupras, RAC; Senior Project Manager
Telephone:	908-704-1691 x223
Fax	908-704-1693
e-Mail	edupras@bhconsultingservices.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not assigned
b) Non-Proprietary Name (USAN): Not Assigned
c) Code Name/#: ME-609
d) CAS Registry Number: 827611-49-4
e) Chem. Type/Submission Priority:
   i. Chem. Type: 3
   ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) (NDA 22-436)

10. PHARMACOL. CATEGORY: Synthetic

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: acyclovir and hydrocortisone, 5% /1%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
_____SPOTS product – Form Completed
___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

Hydrocortisone USP _____ b(4)

International Non-Proprietary Name (INN)
Hydrocortisone (INN, BAN, JAN, USAN)

Other Names
Compendial Names:
Hydrocortisone (USP)
Hydrocortisonum (Ph. Eur.)

CAS Registry Number
CAS: 50-23-7

Molecular Formula and Weight
$C_{21}H_{30}O_5$ 362.46

Chemical Names:

- Pregn-4-ene-3,20-dione, 11,17,21-trihydroxy-, (11)-; (2) Cortisol
- 11β,17,21-Trihydroxypregn-4-ene-3,20-dione

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Under Review	In July 2009	Major amendment submitted 12 June 2009. Review will not

b(4

							be completed until July 2009
[redacted]					Adequate	29 July 2009	Deficiency letter sent to [redacted] 20 July 2009. Response from [redacted] received July 28, 2009
					Inadequate	Generics 19 Jan 2009	Pending Deficiency Letter from 19 Jan 2009
[redacted]					Adequate	29 July 2009	Response to Deficiency Letter of 19 Jan 2009 received July 2009

b(4)

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION
NDA 21-478	Zovirax (Acyclovir) Cream 5%

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Requests for Sample Tubes from Medivir received Nov 2008	Based on internal review, the texture of the material was confirmed as a cream	Nov 2008	Jeffrey B. Medwid, Steve Miller

The Chemistry Review for NDA 22-436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval.

Based the first review of NDA 22436, dated 26 June 2009, this New Drug Application for 'Acyclovir, and Hydrocortisone, 5% /1%" was not recommended for approval due to numerous deficiencies. Except for the site recommendations from the Office of Compliance, all the CMC issues dealing with both DMF holders [redacted] and the sponsor Medivir have been resolved. b(4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None anticipated at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The two active drug substances, acyclovir USP [redacted] and hydrocortisone USP [redacted], are combined into a [redacted] aqueous based cream containing 5% acyclovir and 1% hydrocortisone on a w/w basis. The cream is supplied in either a 2 gram or 5 gram tube. b(4

Acyclovir is an antiviral agent which is highly active in vitro against Herpes Simplex Virus (HSV) types 1 and 2. Acyclovir is phosphorylated after entry into the herpes infected cells to the active compound acyclovir triphosphate. Acyclovir triphosphate acts as an inhibitor of the substrate of the herpes-specified DMA polymerase, preventing further viral DNA synthesis without affecting normal cellular processes.

Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex. It is used topically for its anti-inflammatory effects which suppress the clinical manifestations of the disease in a wide range of disorder where inflammation is a prominent feature.

[redacted] The two actives are combined into the drug product. b(4)

B. Description of How the Drug Product is Intended to be Used

Topical treatment of the cream containing 5% acyclovir and 1% hydrocortisone is used for [redacted] The 2 gram tube is intended to be used over a period of approximately [redacted] 5 days, applying the cream [redacted] 5 times daily to the affected sores. b(4)

C. Basis for Approvability or Not-Approval Recommendation

Since the first review of this NDA was reported (June 26, 2009), revision of both drug substances and the drug product specification have been updated as a result of communications with Medivir, [redacted] All deficiencies have been satisfactorily addressed. b(4)

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls for assuring consistent product quality of the drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the during the expiration dating period.

Inspections of 5 facilities were requested in November of 2008 and are in progress at this time by the office of compliance.

Labels for the tubes and cartons are being revised to remove the initial Tradename that was found to be unacceptable.

III. Administrative

A. Reviewer's Signature

{see electronic signature page}

B. Endorsement Block

{see electronic signature page}

C. CC Block

{see dfs}

89 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Pre-approval Inspections: Summary Report from EES on 31 July 2009, at 12:16 PM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22436/000	**Action Goal:**	
Stamp Date:	01-OCT-2008	**District Goal:**	02-JUN-2009
Regulatory:	01-AUG-2009		
Applicant:	MEDIVIR	**Brand Name:**	ME-609 CREAM
	1400 SOUTH ORANGE AVE	**Estab. Name:**	
	ORLANDO, FL 32806	**Generic Name:**	ACYCLOVIR AND HYDROCORTISONE TOPICAL
Priority:	4	**Product Number; Dosage Form; Ingredient; Potency**	
Org. Code:	530		

Application Comment:

FDA Contacts:	D. ARAOJO	Project Manager	301-796-0669
	J. MEDWID	Review Chemist	301-796-2204
	N. SCHMUFF	Team Leader	301-796-1454

Overall Recommendation:	ACCEPTABLE	on 31-JUL-2009	by E. JOHNSON	(HFD-320)	301-796-3334

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: [redacted] FEI: [redacted] b(4)

[redacted]

DMF No: **AADA:**

Responsibilities: [redacted]

Estab. Comment: THE CHEMIST AT ONDQA (DR. JEFFREY P. MEDWID, 301-796-2204 AT WHITE OAK) WOULD LIKE TO REQUEST TO BE PRESENT FOR THE PAI INSPECTION AT [redacted] TO REVIEW THE [redacted] AND STABILITY DATA IN DETAIL. THERE ARE SEVERAL CRITICAL PARAMETERS INCLUDING MICROSCOPIC EXAMINATION, VISCOSITY AND IMPURITY PROFILES THAT NEED A THOROUGH REVIEW. IF THE PAI OF THE DRUG MANUFACTURER IS AT THE SAME APPROXIMATE TIME, AT THE [redacted] SITE, DR. MEDWID WOULD ALSO REQUEST TO BE PRESENT TO REVIEW THE DRUG PRODUCT MANUFACTURE. (on 05-FEB-2009 by S. ADAMS () 301-827-2443) b(4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	12-NOV-2008				MEDWIDJ
SUBMITTED TO DO	13-NOV-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	10-JAN-2009	GMP Inspection			ADAMSS
INSPECTION SCHEDULED	15-JUL-2009		29-JUL-2009		IRIVERA
DO RECOMMENDATION	31-JUL-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	31-JUL-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: 9615880 FEI: 3001581899

CONTRACT PHARMACEUTICAL LTD

7600 DANBRO CRESCENT
MISSISSAUGA, ON, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Estab. Comment: THE CHEMIST AT ONDQA (DR. JEFFREY B. MEDWID, 301-796-2204 AT WHITE OAK) WOULD LIKE TO REQUEST TO BE PRESENT FOR THE PAI INSPECTION AT CONTRACT PHARMACEUTICAL LTD. (on 13-FEB-2009 by J. MEDWID () 301-796-2204)

b(4)

Profile: OINTMENT,NONSTERILE (INCLUDES CREAM, [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	12-NOV-2008				MEDWIDJ
SUBMITTED TO DO	13-NOV-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	13-NOV-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	31-JUL-2009			ACCEPTABLE	JOHNSONE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	31-JUL-2009			ACCEPTABLE	JOHNSONE
				DISTRICT RECOMMENDATION	

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: [redacted] FEI: [redacted]

[redacted]

DMF No: [redacted] **AADA:**

Responsibilities: [redacted]

Estab. Comment: THE CHEMIST AT ONDQA (DR. JEFFREY B [redacted] 301-796-2204 AT W[redacted] IKE TO REQUEST TO BE PRESENT FOR THE PAI INSPECTION AT [redacted] TO REVIEW THE [redacted] ND STABILITY DATA IN DETAIL. THERE ARE SEVERAL CRITICAL PARAMETERS INCLUDING MICROSCOPIC EXAMINATION, VISCOSITY AND IMPURITY PROFILES THAT NE[redacted] GH REVIEW. IF THE PAI OF THE DRUG MANUFACTURER IS AT THE SAME APPROXIMATE TIME, AT TH[redacted] SITE, DR. MEDWID WOULD ALSO REQUEST TO BE PRESENT TO REVIEW THE DRUG PRODUCT MANUFACTURE. (on 12-NOV-2008 by J. MEDWID () 301-796-2204)
THE CHEMIST AT ONDQA (DR. JEFFREY B [redacted] 301-796-2204 AT W[redacted] LIKE TO REQUEST TO BE PRESENT FOR THE PAI INSPECTION AT [redacted] TO REVIEW THE [redacted] AND STABILITY DATA IN DETAIL. THERE ARE SEVERAL CRITICAL PARAMETERS INCLUDING MICROSCOPIC EXAMINATION, VISCOSITY AND IMPURITY PROFILES THAT NE[redacted] GH REVIEW. IF THE PAI OF THE DRUG MANUFACTURER IS AT THE SAME APPROXIMATE TIME, AT THE [redacted] SITE, DR. MEDWID WOULD ALSO REQUEST TO BE PRESENT TO REVIEW THE DRUG PRODUCT MANUFACTURE. (on 05-FEB-2009 by S. ADAMS () 301-827-2443)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
INSPECTION PERFORMED	28-AUG-2008		28-AUG-2008		JAMES.DUNNIE
SUBMITTED TO OC	12-NOV-2008				MEDWIDJ
SUBMITTED TO DO	13-NOV-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	13-NOV-2008	GMP Inspection			ADAMSS
OC RECOMMENDATION	28-APR-2009			ACCEPTABLE	JOHNSONE
				DISTRICT RECOMMENDATION	

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: [redacted] FEI: [redacted] b(4)

[redacted]

DMF No: [redacted] **AADA:**

Responsibilities: [redacted]

Estab. Comment: SITE CALLED [redacted] NDA FILING. EES CALLS IT [redacted] SPONSOR b(4)
SITES FDA REGISTRATION NUMBER [redacted] (on 05-NOV-2008 by J. MEDWID () 301-796-2204)

Profile: [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	12-NOV-2008				MEDWIDJ
OC RECOMMENDATION	12-NOV-2008			ACCEPTABLE	FERGUSONS
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** [redacted] b(4)

[redacted] b(4)

DMF No: [redacted] **AADA:**

Responsibilities: [redacted]

Estab. Comment: [redacted] b(4)

THE SITE AT [redacted] IN EES, IS LISTED WITH A FDA REGISTRATION NUMBER OF [redacted] IN EES, THE CFN AND FEI NUMBERS ARE CFN [redacted] & FEI FOR THIS SITE. (on 12-NOV-2008 by J. MEDWID () 301-796-2204)

Profile: [redacted] **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	12-NOV-2008				MEDWIDJ
SUBMITTED TO DO	13-NOV-2008	GMP Inspection			ADAMSS
ASSIGNED INSPECTION TO IB	15-JAN-2009	GMP Inspection			ADAMSS
INSPECTION SCHEDULED	12-JUN-2009		18-JUN-2009		IRIVERA
DO RECOMMENDATION	31-JUL-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	31-JUL-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
DA 22436	ORIG 1	MEDIVIR AB	ME-609 CREAM

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

/s/

JEFFREY B MEDWID
07/31/2009

NORMAN R SCHMUFF
07/31/2009

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Anti-Viral Products
NDA:	22-436
Applicant:	Medivir
Stamp Date:	30-Sep-2008
PDUFA Date:	30-Jul-2008
Trademark:	Lipsovir
Established Name:	Acyclovir 5% and hydrocortisone 1% cream
Dosage Form:	Cream
Route of Administration:	Topical
Indication:	Treatment of early signs and symptoms of recurrent herpes labialis (cold sores) to prevent the development and reduce the duration of ulcerative cold sores in adults and adolescents (12 years of age and older).
PAL:	Stephen Miller

	YES	NO
ONDQA Fileability:	x	☐
Comments for 74-Day Letter	☐	x

Summary and Critical Issues:

A. Summary

This IND was first submitted on 7/13/99 and has undergone an extensive IND review process. A full description of that process can be found at:
T:\DPA2\Branch 4\DAVP Applications\58 500 ME-609 Cream GLunn\58,500 acyclovir-hydrocortisone cream.doc

In general sufficient information has been submitted during the IND process to support an NDA. However, the following items have been identified as potential NDA problems and should be given special attention by the reviewer.

- The sponsor should be asked: Please provide a sample of the ME-609 cream so that we can assess its viscosity. This is related to nomenclature. Name of "cream" or "lotion" depends on the viscosity.

- As pointed out by the sponsor in response to IND Amendment 036 FDA replied "If the results for three process validation batches show that they are homogeneous routine homogeneity testing of the drug product will not be required." Also FDA accepted Medivir's proposal [redacted] in the FDA fax of 1/26/08. However this was an error. During NDA

b(4)

b(4)

review it should be made clear that [redacted] should continue until a large body of data (as defined by Derm and Dental) is accumulated. [redacted] should be via a Prior-Approval Supplement.

b(4)

- Some batches were inadvertently made with [redacted] and [redacted] citric acid (see IND Amendment N-092) rather than the commercial formulation value of [redacted]. The reviewer should check to make sure that only stability data from batches with [redacted] citric acid is used to support the stability of the commercial product.

b(4)

The NDA submission appears to contain all the expected CMC sections. Since sufficient information has been submitted during the IND process the NDA should contain sufficient information for a complete and thorough review.

B. Recommendation:

This NDA is fileable from a CMC perspective. A CMC reviewer should be assigned.

George Lunn

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

/s/

George Lunn
1/29/2009 11:19:51 AM
CHEMIST

This is the IQA for NDA 22-436. See also review of IND 58,500. No PM action required

Norman Schmuff
1/29/2009 06:06:51 PM
CHEMIST