

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-793

CHEMISTRY REVIEW(S)



NDA 50-793

ClindesseTM (clindamycin phosphate) Vaginal Cream, 2%

KV Pharmaceutical

**Dorota Matecka
Division of Special Pathogen and Immunologic Drug
Products, HFD-590**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability.....	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment.....	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE [Clindamycin phosphate, _____].....	12
S.1 General Information [Clindamycin phosphate, _____].....	12
S.2 Manufacture [Clindamycin phosphate, _____].....	13
S.3 Characterization [Clindamycin phosphate, _____].....	13
S.4 Control of Drug Substance [Clindamycin phosphate, _____].....	14
S.5 Reference Standards or Materials [Clindamycin phosphate, _____].....	18
S.6 Container Closure System [Clindamycin phosphate, _____].....	18
S.7 Stability [Clindamycin phosphate, _____].....	19
P DRUG PRODUCT [Clindamycin phosphate vaginal cream].....	19
P.1 Description and Composition of the Drug Product [Clindamycin phosphate vaginal cream].....	19
P.2 Pharmaceutical Development [Clindamycin phosphate vaginal cream].....	20
P.3 Manufacture [Clindamycin phosphate vaginal cream].....	24
P.4 Control of Excipients [Clindamycin phosphate vaginal cream].....	30
P.5 Control of Drug Product [Clindamycin phosphate vaginal cream].....	32
P.6 Reference Standards or Materials [Clindamycin phosphate vaginal cream].....	51
P.7 Container Closure System [Clindamycin phosphate vaginal cream].....	51
P.8 Stability [Clindamycin phosphate vaginal cream].....	54
A APPENDICES	59



CHEMISTRY REVIEW



R	REGIONAL INFORMATION	59
R.1	Executed Batch Records.....	59
R.2	Comparability Protocols.....	60
R3	Methods Validation Package.....	69
II.	Review Of Common Technical Document-Quality (CTD-Q) Module 1	69
A.	Labeling & Package Insert	69
B.	Environmental Assessment Or Claim Of Categorical Exclusion	70
III.	List Of Deficiencies	70



Chemistry Review Data Sheet

1. NDA 50-793
2. REVIEW # 1
3. REVIEW DATE: 18-Nov-2004
4. REVIEWER: Dorota Matecka
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-Oct-2003
C	14-Jan-2004
IR	31-Mar-2004
BC	4-Apr-2004
IR	30-Jun-2004
IR	19-Aug-2004
AC	20-Aug-2004
BC	14-Sep-2004
BC	8-Oct-2004
IR	26-Oct-2004
BC	5-Nov-2004
IR	10-Nov-2004
BC	11-Nov-2004
IR	16-Nov-2004
BC	17-Nov-2004



CHEMISTRY REVIEW



Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-Oct-2003
C	14-Jan-2004
BC	31-Mar-2004
AC	20-Aug-2004
BC	14-Sep-2004
BC	8-Oct-2004
BC	5-Nov-2004
BC	11-Nov-2004
BC	17-Nov-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	KV Pharmaceutical
Address:	2503 South Hanley Road St. Louis, Missouri 63144
Representative:	Herbert G. Luther, Ph.D.
Telephone:	(314) 645-6600

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Clindesse Vaginal Cream
- b) Non-Proprietary Name (USAN): clindamycin phosphate vaginal cream
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: antibacterial

11. DOSAGE FORM: vaginal cream



CHEMISTRY REVIEW



Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 2%
13. ROUTE OF ADMINISTRATION: vaginal
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

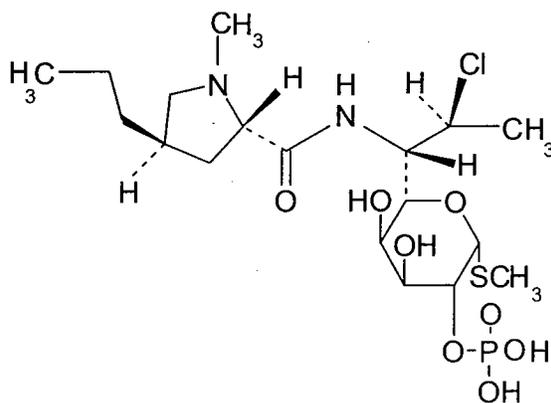
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 7(S)-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo- α -D-galacto-octopyranoside 2-dihydrogen phosphate

Molecular weight: 504.96 grams per mole

Molecular formula: $C_{18}H_{34}ClN_2O_8PS$

Chemical structure:





CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
				1	Adequate	18-Nov-2004	N/A
				2	N/A	N/A	N/A
				4	N/A	N/A	N/A
				3 and 4	Adequate	27-Sep-2000	

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,397	IND (KV Pharmaceutical) for clindamycin phosphate vaginal cream, 2%
NDA	19,881	Gynazole (butoconazole nitrate) Vaginal Cream, 2%
NDA	50-680	Cleocin (clindamycin phosphate) Vaginal Cream, 2%



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	1-Sep-2004	Shawnte L. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMETS	Acceptable	10-Aug-2004	Linda Y. Kim-Jung, Pharm.D.
EA	N/A (request for a categorical exclusion)		
Microbiology	Acceptable	26-May-2004	Brian S. Riley, Ph.D.



The Chemistry Review for NDA 50-793

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

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

N/A

II. Summary of Chemistry Assessments

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

Clindamycin phosphate is a water soluble ester of semi-synthetic antibiotic produced by 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

For the majority chemistry, manufacturing, and controls (CMC) for the clindamycin phosphate drug substance, the reference is made to the DMF [REDACTED]

The initial review of this DMF revealed a number of deficiencies and DMF [REDACTED] was found inadequate to support this NDA (refer to review # 1 dated 8-Dec-2003). The U.S. agent for DMF [REDACTED] could not be initially identified and was eventually located by the NDA applicant via a correspondence to this NDA dated 15-Jan-2004 (received 20-Jan-2004). The deficiency letter was forwarded to the DMF holder (via their U.S. agent) on 21-Jan-2004. The DMF holder responded to the noted deficiencies on 29-Jul-2004. As a result of further communications with the DMF holder, DMF [REDACTED] was eventually found adequate to support this NDA (refer to the DMF review # 2 dated 18-Nov-2004).

The drug product, Clindesse Vaginal Cream (clindamycin phosphate vaginal cream) is a soft, off-white, homogeneous cream formulated as a water-in-oil emulsion, which is intended to produce a long term local residence of the formulation at the vaginal mucosa with minimal systemic absorption.

Each gram of cream contains 20 mg of clindamycin base (provided by clindamycin phosphate) and a preservative system consisting of methylparaben at [REDACTED] by weight and propylparaben at [REDACTED] by weight. Clindamycin phosphate vaginal cream, 2%, is not sterile, however, it meets the criteria of the USP Preservative Effectiveness test. The submission "was recommended for approval on the basis of product quality microbiology" per the review conducted by the OPS Microbiology Team (HFD-805).

Executive Summary Section

The drug product is packaged in a _____ applicator, which delivers approximately 5 gram of the cream. The applicator is placed in a _____ tray for physical protection, and wrapped in a _____ pouch.

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

Clindesse (clindamycin phosphate) Vaginal Cream, 2%, is indicated for the treatment of bacterial vaginosis (BV).

Clindesse (clindamycin phosphate) Vaginal Cream, 2% is supplied in one pre-filled plastic applicator. One full applicator delivers approximately 5-gram of clindamycin phosphate vaginal cream, 2%, which should be administered intravaginally at the bedtime.

The storage conditions statement recommends the storage at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Avoid heat above 30°C (86°F). The expiration dating for the product is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The user fee goal date for this NDA was extended from the initial August 31, 2004 to the current November 30, 2004. This extension was due to the major NDA amendment (AC) dated 20-Aug-2004 and received 24-Aug-2004) containing the responses to the NDA deficiencies. The other reasons for the three-month extension included a delayed (due to the DMF holder's request) GMP inspection of the clindamycin phosphate drug substance manufacturing facility, in addition to the delayed response to the DMF _____ (clindamycin phosphate drug substance) deficiency letter (as described above, in section A of this summary).

The NDA submission and amendments provide adequate information on the chemistry, manufacturing and controls for the production of Clindesse (clindamycin phosphate) Vaginal Cream, 2%. During the review several issues, including the following were resolved.

Several revisions were made in the specification of the drug substance and the drug product during the course of the review. Specifically, the test and acceptance criteria for impurities, residual solvents, and particle size in the drug substance specification were added. In addition, the test and provisional acceptance criterion for viscosity were added in the drug product specification. Also, the acceptance criteria for impurities in the drug product were revised.

The trade name "Clindesse" was found acceptable for this product. The proposed labeling for Clindesse (clindamycin phosphate) Vaginal Cream, 2%, is very similar to the labeling of the approved Cleocin (clindamycin phosphate) Vaginal Cream, 2%. Since Clindesse Vaginal Cream is not tested for pH (it is a water-in-oil emulsion), as recommended by the USP monograph for clindamycin phosphate vaginal cream, the following statement was included in the labeling of this product: "Does not comply with the pH testing of the USP monograph for clindamycin phosphate vaginal cream".



III. Administrative

A. Reviewer's Signature

DFS

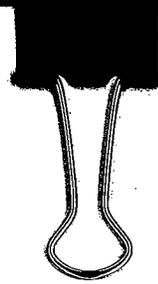
B. Endorsement Block

Dorota Matecka/Date

Mark Seggel/Date

Christina Chi/Date

C. CC Block



69 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

Dorota Matecka
11/27/04 11:36:57 PM
CHEMIST

Mark Seggel
11/29/04 09:06:14 AM
CHEMIST