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APPLICATION NUMBER:

50-793

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 50-793	Submission Date(s): October 31, 2003
Brand Name	[redacted]
Generic Name	Clindamycin Phosphate Vaginal Cream, 2%
Reviewer	Seong H. Jang, Ph.D.
Team Leader	Phil M. Colangelo, Pharm.D., Ph.D.
Clinical Review Division	DSPIDP (HFD-590)
Sponsor	KV Pharmaceutical Company
Submission Type; Code	N
Formulation; Strength(s)	Vaginal Cream: 2%
Proposed Indications	Bacterial Vaginosis

I. Executive Summary

The sponsor submitted this NDA for its product, [redacted] (Clindamycin Phosphate Vaginal Cream, 2%), for one-dose treatment of bacterial vaginosis. The product contains the same active ingredient, clindamycin phosphate, as Pharmacia and Upjohn's Cleocin® Vaginal Cream 2% (NDA 50-680) and the same vehicle as KV Pharmceutical's Gynazole-1® (NDA 19-881). This vehicle is effective for intravaginal delivery of clindamycin phosphate as a single dose rather than the multiple daily doses required with Cleocin® vaginal cream 2%. The reduced dosing frequency offers the potential to increase patient compliance for the intravaginal treatment of bacterial vaginosis. The approval of this application depends both on the Agency's finding of safety and effectiveness for the previously approved Cleocin® Vaginal Cream and on clinical studies conducted by the sponsor evaluating the safety and efficacy of [redacted]

The sponsor also conducted a relative bioavailability study comparing the systemic exposure to clindamycin from the [redacted]® product to that from Cleocin® Vaginal Cream in healthy female volunteers (Study KVP-214). The results of this study showed that *the systemic absorption of clindamycin following intravaginal administration of* [redacted] *appeared to be substantially less and slower compared with Cleocin® Vaginal Cream,* supporting little systemic effects of clindamycin after a single intravaginal dose of [redacted]. **The study design and results are acceptable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewer.**

I-1. Recommendation

The Clinical Pharmacology and Biopharmaceutics information in this application is sufficient to support the approval of [redacted]

I-2. Phase IV Commitment

Not applicable

I-3. Labeling Comments

Labeling comments from the OCPB reviewers are incorporated into the final label (version 08/05/2004) in Appendix 1.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Concurrence

Phil Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Clinical Pharmacology and Biopharmaceutics Review

This application includes a method validation report for clindamycin assay in human plasma, a pilot study report for systemic bioavailability of intravaginal [redacted]®, and a relative bioavailability study comparing the systemic exposure to clindamycin from the KV product, [redacted], to that from Cleocin®. The pilot study report was not reviewed here.

I. Formulation and composition

[redacted] (clindamycin phosphate) Vaginal Cream, 2.0% is a sustained release vaginal cream product containing 2% Clindamycin phosphate. It is a soft off-white, homogenous cream, free from crystal formation, foreign matter, and lumps. Each gram of cream contains 20.0 mg of Clindamycin base (provided by clindamycin phosphate), [redacted] of methylparaben and [redacted] of propylparaben. The finished product is packaged into a [redacted] applicator consisting of five assembled components (main body, internal plunger, external plunger, ring, and tip). The applicator is prefilled with a 5-gram dose of cream. The applicator is placed in a [redacted] tray for physical protection, and wrapped in a [redacted] pouch. The sealed construction of the prefilled applicator allows no product contact with the pouch or tray.

Table 1. Composition of Clindamycin Phosphate Vaginal Cream, 2.0%

KV Stock #	Component	Grade	Function	% w/w	Batch Size (kg)	Mg/Dose[1]
2-1111	Clindamycin Phosphate	USP	Active Ingredient	[redacted]	[redacted]	[redacted]
8-51	Purified Water	USP	[redacted]	[redacted]	[redacted]	[redacted]
8-47	Sorbitol Solution	USP	[redacted]	[redacted]	[redacted]	[redacted]
8-735	Edetate Disodium	USP	[redacted]	[redacted]	[redacted]	[redacted]
8-216	Mineral Oil	USP	[redacted]	[redacted]	[redacted]	[redacted]
8-1590	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8-511	Polyglyceryl-3-Oleate	---	[redacted]	[redacted]	[redacted]	[redacted]
8-615	Glycerol Monoisosteatate	---	[redacted]	[redacted]	[redacted]	[redacted]
8-548	Microcrystalline Wax	NF	[redacted]	[redacted]	[redacted]	[redacted]
8-1	Methylparaben	NF	[redacted]	[redacted]	[redacted]	[redacted]
8-2	Propylparaben	NF	[redacted]	[redacted]	[redacted]	[redacted]
8-672	Silicon Dioxide, Hydrophobic	---	[redacted]	[redacted]	[redacted]	[redacted]
			Total	100.0	[redacted]	5000.0

1. Each dose is 5 grams (5,000 mg) of vaginal cream. Each component's percentage is multiplied by the dose to calculate the numerical component amount per dose of the final product.
2. The amount of active ingredient and water to be added is calculated per batch based on the assay and water content of the raw material.

II. Bioanalytical Methodology

Plasma concentrations of clindamycin were measured using a validated LC/MS/MS method. The method was linear from 0.2 (LLOQ) to 80 (ULOQ) ng/mL. The precision (CV) for clindamycin at the ULOQ and at the LLOQ was 1.7% and 3.3%, respectively. The accuracy for

clindamycin at the ULOQ and at the LLOQ was 105% and 107%, respectively. The intra-day and inter-day precisions and accuracies were summarized I Table 1.

Table 1. Precision and accuracy of the LC/MS/MS for clindamycin in plasma.

	60 ng/mL	6 ng/mL	0.5 ng/mL
Intra-day			
Precision	1.1-3.1	1.0-3.1	1.6-6.2
Accuracy	104-106	87.7-95.8	103-107
Inter-day			
Precision	2.3	4.5	4.0
Accuracy	105	92.7	107

During the validation, blank plasma samples from 6 donors were evaluated. There were no interfering peaks in the blank plasma at the retention times of clindamycin or the internal standard, omeprazole. Interference from aspirin, acetaminophen, chlorpheniramine maleate, ibuprofen, and pseudoephedrine hydrochloride was also evaluated under clindamycin assay conditions. No interference was observed at the retention time of clindamycin or the internal standard.

There were 2 sets of QC samples at high (60 ng/mL) and low (0.5 ng/mL) concentrations injected using 4 different plasma matrices to study the matrix effect. The accuracy for the plasma matrices for the high (60 ng/mL) and low (0.5 ng/mL) concentration QC sample was in the range of 102 to 112%, indicating that there is no significant matrix effect.

Reviewer's comments: The intra- and inter-day precisions and accuracies are within acceptance criteria, i.e., ±15% of nominal value, except at the LLOQ where the allowable limit is ±20% of nominal value. In general, the assay validation methods and the results are acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.

III. Relative bioavailability study

Title: A randomized, single-dose, two-way crossover relative bioavailability study of clindamycin vaginal cream formulations in normal, healthy women (Study # KVP-214)

Objective: To compare the relative bioavailability of KV clindamycin vaginal cream 2% to that of Cleocin® Vaginal Cream 2% after a single, 5 gm intravaginal dose in healthy women.

Study Design: Open-label, balanced, randomized, single-dose, two-period, two-treatment, two-sequence crossover in healthy female volunteers

Treatment:

A: Clindamycin Vaginal Cream 2%, Lot No. DR/139/19
(manufactured by KV Pharmaceutical)

B: Cleocin® Vaginal Cream 2% Lot No. 64HRR
(manufactured by Pharmacia and Upjohn)

Subjects received a single 5 gm dose of Treatment A or Treatment B on two occasions (Periods 1 and 2). The test (A) and reference (B) formulations were administered according to a randomized code. All doses were administered after an overnight fast.

Duration of Treatment: Following a single dose on Day 1 Treatment Period 1, subjects remained in the study unit until the 36-hour blood sample was collected. They then returned to the unit for the 48-, 72-, and 96-hour blood samples. After a 14-day washout period, the same subjects returned for Treatment Period 2. Each subject received a single dose in each of two treatment periods.

Subject Characteristics: Twenty subjects were recruited for this study and all subjects were healthy adult, female subjects, in the age range of 18 to 66 (mean age 43) years. The weight range of the subjects was 48 to 92 kg (mean height 160 cm, mean weight 66 kg). Of 20 subjects, 19 subjects completed the clinical portion of the study. One subject failed to return for the second period.

Pharmacokinetic parameters: The bioavailability of clindamycin from the KV cream relative to Cleocin was assessed by measuring serial plasma clindamycin concentrations after administration of each treatment. Blood samples for measurement of plasma clindamycin concentration were collected before and 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 30, 36, 48, 72, and 96 hours after drug administration in each period. Plasma concentrations of clindamycin were determined using a validated LC/MS/MS method with a lower limit of quantification (LLOQ) of 0.2 ng/mL. Maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), terminal half-life ($T_{1/2}$) and area under the serum concentration time from zero to the last time with a concentration >LLOQ (AUC_{0-t}) and to infinity (AUC_{inf}) were estimated using non-compartmental analysis. Mean values for C_{max} and AUCs for the test formulation were compared to those of the reference formulation using an analysis of variance statistical model with calculation of 90% confidence intervals for the geometric mean ratio of the test formulation to the reference formulation. C_{max} and the AUCs were natural log-transformed before analysis. Subjects who received study medications and completed both the test and the reference treatment periods were included in the analysis.

Safety Parameters: All subjects (20) who received at least one dose of study medication were included in the assessment of safety. Hematology, serum chemistry, and urine analysis were conducted at screening. Sitting vital signs (blood pressure, pulse, temperature) were evaluated prior to administration of the dose for each study period. Adverse events that occurred after study drug was taken were recorded. Female subjects of childbearing potential had a urine pregnancy test prior to each dosing day to confirm the subject was not pregnant.

Pharmacokinetic Results: The pharmacokinetic parameters of clindamycin after intravaginal administration of KV Pharmaceutical's clindamycin vaginal cream 2% and Cleocin® Vaginal Cream 2% (Pharmacia and Upjohn) and their corresponding plasma concentration-time profiles are demonstrated in Table 2 and Figure 1, respectively. Plasma concentration and pharmacokinetic parameters after administration of both formulations were highly variable. Coefficients of variation for C_{max} and AUC ranged from 86% to 154% and 96% to 127% for the test and reference formulations, respectively. The mean plasma clindamycin concentrations

after intravaginal administration of the KV cream were substantially lower that those after administration of Cleocin® as were mean values for C_{max} and the AUCs. The bioavailability of clindamycin from the KV cream was 7.52% based on C_{max} and 12.4% based on AUC_{0-t} or AUC_{inf}. In summary, the systemic exposure to clindamycin after intravaginal administration of the KV vaginal Cream 2% was ~12% of that after administration of Cleocin® Vaginal Cream 2%.

Table 2. Mean clindamycin pharmacokinetic parameters after intravaginal administration of KV and Cleocin® Vaginal cream 2% to healthy female volunteers and the relative bioavailability comparison.

Parameters	KV	Cleocin®	Ratio (%)	
			Point Estimate (KV/Cleocin®)	90% confidence Interval
C_{max} (ng/mL)[a]	6.58±10.1 (0.831 to 39.4)[a]	86.5±110 (8.05 to 408)	7.52	[5.26, 10.7]
T_{max} (h)[b]	20 (1 to 72)[b]	6 (2 to 36)		
AUC_{0-t} (ng·hr/mL)[a]	140±137 (27 to 539)	1,226±1,191 194 to 4466)	12.4	[8.72, 17.7]
AUC_{inf} (ng·hr/mL)[a]	175±150[c] (38.6 to 541)	1,238±1,191 (199 to 4475)	12.4	[7.89, 19.5]
$T_{1/2}$ (h)[a]	19.2±15.4[c] (5 to 65.5)	11.3±5.76 (3.2 to 23.7)		

[a]: Mean ±SD (range), [b]: Median (range)
[c]: A terminal phase was not determined in five of 20 subjects. Thus, the values are based on 15 subjects.

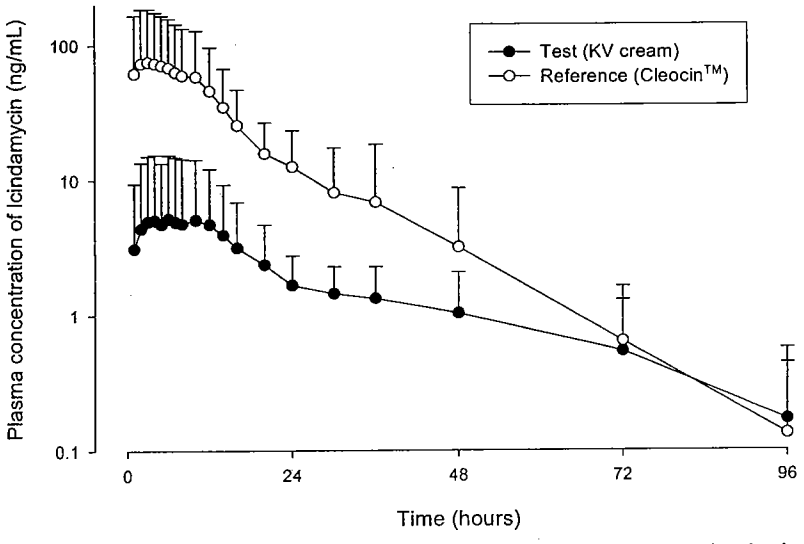

Figure 1. Mean plasma concentrations after intravaginal administration of KV and Cleocin® Vaginal Cream 2% to healthy female volunteers.

Reviewer's comment:

1. The mean peak serum clindamycin concentration obtained following vaginal administration of Cleocin® in this study is substantially higher compared with that found in the current label of Cleocin®; 86.5 ng/mL (range 8 to 408 ng/mL) vs. 18 ng/mL (range 4 to 47 ng/mL). The reason for this difference was not addressed in this submission. Nevertheless, the peak serum clindamycin concentration following vaginal administration of [redacted] (6.6 ng/mL, range 0.8 to 39 ng/mL) was considered to be lower compared with that found in the current label of Cleocin®. The greater value of T_{max} and terminal half-life following [redacted] compared with Cleocin® indicate the slower systemic absorption of clindamycin following [redacted] compared with Cleocin®. Collectively, the systemic absorption of clindamycin following intravaginal administration of [redacted] seems substantially less and slower compared with Cleocin®.

2. Another concern regarding systemic absorption of clindamycin from [redacted] is whether the absorption is changed in patients with bacterial vaginosis or not. This issue was not addressed in this application. However, according to the current label of Cleocin®, the systemic absorption of clindamycin from Cleocin® in women with bacterial vaginosis was slower and less variable than that observed in healthy females. Thus, systemic absorption of clindamycin from [redacted] in patients with bacterial vaginosis seems not greater than that in healthy women. Accordingly, the lack of information regarding absorption in women with bacterial vaginosis does not appear to be meaningful to the overall conclusions.

Safety Results: There were 18 adverse events in nine subjects during this study. There were 8 instances of headache, 4 of vomiting, and 1 each of body aches, abdominal fullness, hypotension, hypertension, elevated temperature, and lightheadedness. Twelve adverse events were considered mild, 4 were considered moderate, and two were considered severe. Both severe adverse events were headaches and were considered remotely related to study drug. One adverse event was considered not related, 1 unlikely related, 15 remotely related, and 1 possibly related to treatment. All adverse events resolved without sequel or treatment.

Conclusions:

1. The systemic absorption of clindamycin after intravaginal administration of the KV vaginal Cream 2% was substantially slower than that after administration of Cleocin® Vaginal Cream 2%.
2. The systemic exposure to clindamycin after intravaginal administration of the KV vaginal Cream 2% was ~12% of that after administration of Cleocin® Vaginal Cream 2%.
3. The intravaginal dose of [redacted] was safe and well tolerable.
4. Overall, considering the safety of the previously approved Cleocin®, the limited systemic absorption of clindamycin from [redacted] compared with Cleocin® supports that there would be minimal systemic effects of clindamycin after administration of the single intravaginal dose of [redacted] cream.

10 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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Seong Jang
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Phil Colangelo
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