CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-767

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**50-767**
Submission Date:	October 13, 1998 AUG 9 1999
Drug Product:	Clindamycin Phosphate Vaginal Suppository, 100 mg
Trade Name:	CLEOCIN® Vaginal Ovule
Sponsor:	Pharmacia&Upjohn Kalamazoo, MI
Submission Type:	Original NDA
Category:	S (10 Month)
OCPB Reviewer:	Philip M. Colangelo, Pharm.D., Ph.D.
OCPB Log-In:	October 20, 1998

I. BACKGROUND / INTRODUCTION

Clindamycin is a semi-synthetic antibiotic and its spectrum of activity includes gram-positive aerobes (other than enterococci) and gram-positive and gram-negative anaerobes. Clindamycin phosphate has been approved for marketing in the U.S. in several formulations since the early 1970's, including a sterile solution for IV or IM administration, and as a topical solution, gel, and lotion for external use. Clindamycin has also been approved and marketed for oral use as capsules (HCl salt) and flavored granules (palmitate salt).

Most notably, clindamycin phosphate was recently approved by prescription only (August 1992) as a 2% (100 mg/5 g dose) vaginal cream for the treatment of bacterial vaginosis (BV). The currently recommended duration of treatment with the vaginal cream is either 3 or 7 consecutive days in non-pregnant female patients and 7 consecutive days in pregnant patients.

This current submission seeks market approval for a clindamycin phosphate vaginal suppository for the same indication as the 2% vaginal cream, i.e., treatment of bacterial vaginosis in females. It is also intended for prescription use only. The suppository contains clindamycin phosphate equivalent to 100 mg free base clindamycin [redacted]. Once inserted into the vagina, the suppository is designed to melt at body temperature and release drug into the vaginal cavity for a local effect. The suppository was therefore developed as an alternative and potentially more convenient dosage form, as compared to the vaginal cream, for the treatment of BV.

At the time of the NDA submission, the clindamycin phosphate vaginal suppository has not been approved or marketed in any country [redacted].

II. INDICATIONS and DOSAGE

The proposed labeling for this product is provided as Appendix 1 with this review. The indication and recommended dose are summarized as follows:

> One CLEOCIN Vaginal Ovule (100 mg clindamycin/2.5 g suppository) administered intravaginally, preferably at bedtime, for 3 consecutive days for the treatment of bacterial vaginosis.

III. NDA SUMMARY

1. CLINICAL PHARMACOLOGY

Item 6: Human Pharmacokinetics and Bioavailability of this submission contained one drug absorption/bioavailability study, **M/1114/0003. A more detailed review of this study is provided in Appendix 2 and is available upon request from the OCPB reviewer or the Division of Pharmaceutical Evaluation 3 (OCPB, DPE 3).**

The primary objective of the study was to evaluate the absolute bioavailability (BA) of the vaginal ovule by comparison to a reference treatment with intravenous (IV) clindamycin phosphate. A secondary objective was to assess the relative BA of the ovule compared to the approved and marketed clindamycin vaginal cream 2%.

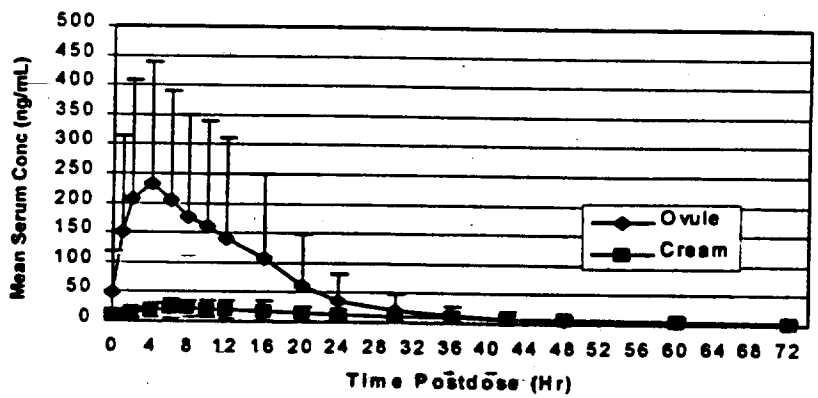
The study was conducted in 12 healthy young female subjects who received in cross-over fashion the 100 mg vaginal ovule (**A**) or the 2% (100 mg/dose) vaginal cream (**B**) QD for 3 consecutive days. In the 3rd treatment arm (**C**), 11 of these female subjects received a *single sub-therapeutic 100-mg IV dose* of clindamycin over 4 minutes. The serum PK of clindamycin was determined after the 3rd consecutive doses of the intravaginal treatments **A** and **B**, and after the single IV dose.

RESULTS:

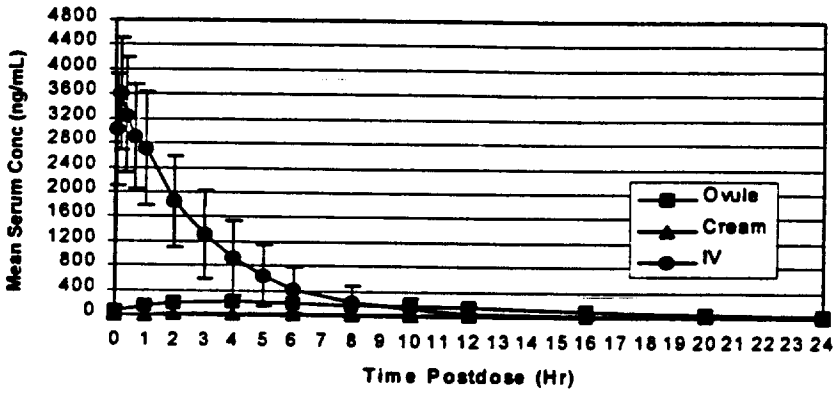
The mean (SD) serum clindamycin concentration-time profiles for the three treatments are illustrated in the two figures below. Mean serum clindamycin concentrations for the vaginal treatments were significantly higher following administration of the vaginal ovule than those for the cream from the time of the 3rd dose on Day 3 through 16 hr postdose ($p < 0.05$). At 24 hrs after the 3rd dose, mean (SD) serum drug concentrations for the ovule vs. cream were 35 ± 46 ng/mL vs. 12 ± 8 ng/mL, respectively ($p = 0.0982$). The inter-subject variability in the mean serum clindamycin concentrations was also substantially higher for the ovule (i.e., %RSD 90-146%) than that of the cream (i.e., %RSD 61-89%).

Mean serum drug levels were substantially higher out to ~6 hrs after a *single sub-therapeutic 100 mg IV clindamycin dose* as compared to either the vaginal ovule or vaginal cream treatments.

Mean (SD) Serum Clindamycin Concentrations Following QD Administration of 100 mg Clindamycin Phosphate Vaginal Ovule or Vaginal Cream for 3 Days (N = 12)



Mean (SD) Clindamycin Serum Concentrations Following Single 100 mg IV Dose (N = 11) and After 100 mg QD Vaginal Ovule or Cream for 3 Days (N = 12)



The PK results are summarized in the following table for the intravaginal and IV treatments.

Serum Clindamycin Pharmacokinetic Parameters on Day 3 Following Intravaginal Administration of 100mg Doses of Either Clindamycin Phosphate Vaginal Ovule or Cream QD for 3 Days (N = 12)

Parameter	Vaginal Ovule (Treatment A)		Vaginal Cream (Treatment B)		p-value
	Mean ± SD (% RSD)	Range	Mean ± SD (% RSD)	Range	
AUC_{0-24} (ng.hr/mL)	3182 ± 3081 (97%)		417 ± 282 (68%)		.0044
Cmax (ng/mL)	270 ± 244 (90%)		23.8 ± 15.9 (67%)		.0039
Tmax (h)	4.6 ± 2.6 (56%)		8.0 ± 4.0 (50%)		.0701
T½ (h)*	11.2		14.4		NC
F_{abs} (%)**	30.5 ± 21.4 (70%)		4.26 ± 3.66 (86%)		.0004

* Harmonic mean
NC = Not Calculated
** Absolute bioavailability calculated as Day 3 AUC(0-24)vag/AUC(0-∞)iv; N = 11

Clindamycin Pharmacokinetic Parameters Following Intravenous Administration of a Single 100mg Dose of Clindamycin Phosphate (N = 11)

Parameter	Mean ± SD (% RSD)	Range
$AUC_{0-\infty}$ (ng.hr/mL)	10,600 ± 5630 (53%)	
Cmax (ng/mL)	3720 ± 910 (24%)	
Tmax (hr)	0.22 ± 0.16 (73%)	
T½ (hr)*	1.72	

* Harmonic mean

CONCLUSIONS:

Overall, the PK results suggested that both the rate (i.e., based on Cmax and Tmax) and extent (i.e., based on AUC) of systemic absorption from intravaginal administration of the clindamycin vaginal ovule was greater than that from the vaginal cream in the 12 healthy female subjects studied. Intravaginal administration of the ovule at the proposed dosage regimen for treatment of bacterial vaginosis, i.e., 100 mg ovule for 3 consecutive days, resulted in significantly higher systemic absorption/systemic drug exposure than that following the same dosage regimen with the vaginal cream. The mean absolute bioavailability (F_{abs}) of the ovule, as compared to a ***single sub-therapeutic 100 mg IV dose of clindamycin***, was significantly greater at 30% versus 4% for the cream ($p = 0.0004$). Thus, systemic absorption was approximately 7-fold greater after intravaginal administration of the ovule compared to the vaginal cream.

The systemic absorption/PK of clindamycin from the clindamycin phosphate vaginal cream determined in the healthy females in this study was consistent with that reported by the sponsor in previous bioavailability studies and in the approved labeling for the vaginal cream in both healthy subjects and patients with bacterial vaginosis.

The between subject variability in the estimates of AUC, Cmax, and F_{abs} was substantial for both intravaginal treatments, with %RSD values ranging from ~70 to ~100%. Individual AUC(0-24) values for the ovule varied 27-fold over a range from [redacted] and Cmax values for the ovule varied 25-fold over a range from [redacted] For the cream, the individual values of AUC(0-24) and Cmax varied to a lesser extent, i.e., 9-fold. Estimates of F_{abs} for the ovule varied 11-fold over a range from 6.5 up to 70%, and varied 9-fold for the cream from 1.6 up to 15%.

*One subject **(No. 12)** had either the highest or nearly the highest extent of overall systemic exposure to clindamycin after all three treatments (i.e., vaginal **Treatments A and B** and IV **Treatment C**). For example, the estimates of AUC (i.e., 11,423 ng.hr/mL) and Cmax (i.e., 666 ng/mL) for this subject following ovule administration were substantially greater than the overall mean values for this treatment. One potential explanation for the higher than average drug exposure in this subject appeared to be reduced drug elimination, as evidenced by the prolonged estimates of the apparent T½ for the ovule (22 hrs) and cream (30 hrs). This subject also had the lowest systemic clearance value (CL = 3.9 L/hr) and the most prolonged T½ (3.0 hrs) after IV clindamycin administration.*

Despite the greater extent of systemic drug exposure after treatment with the vaginal ovule, vaginal cream, and IV clindamycin, Subject 12 completed all three treatments. Three adverse events of mild severity were reported with the ovule, but were considered NOT to be treatment related (i.e., eczema, nasal discharge, and cough). No adverse events were reported with the vaginal cream or IV treatments for this subject. A noteworthy finding on screening was that Subject 12 was judged to have an abnormal pelvic exam due to a past history of hysterectomy. It is not known whether this may have also contributed to the higher degree of systemic drug exposure.

Despite the increased systemic absorption observed with the vaginal ovule over the cream, systemic exposure to clindamycin was still substantially higher following ***single IV administration of a sub-therapeutic dose*** of clindamycin. The mean AUC following the single 100 mg IV dose was ~3-times that of the ovule, while the mean Cmax for the IV dose was ~14-times that of the ovule. The mean AUC and Cmax following the IV clindamycin dose was ~25-times and ~150-times, respectively, of that of the vaginal cream.

All reported adverse events (AE's) with the ovule were considered to be either mild or moderate and no adverse events were reported as severe. Although administration of both vaginal ovule and vaginal cream for 3 consecutive days appeared to be well tolerated by all subjects, there were more AE's associated with administration of the vaginal ovule. In particular, there were

treatment associated vaginal AE's (burning and/or pruritis) that occurred only with the ovule (4/12 subjects) but not with the vaginal cream.

Pharmacokinetic (PK) comparisons indicated that overall systemic exposure to clindamycin from the vaginal ovule is considerably lower than that from recommended oral (i.e., lower by a factor of ~2-20) and IV (i.e., lower by a factor of ~40-50) doses.

*Based on these comparisons and the results from this present study, it is expected that intravaginal administration of the ovule would not cause any additional safety concerns, **with respect to systemic adverse events**, beyond those that have already been identified and reported with systemic administration of clindamycin.*

2. FORMULATION SUMMARY

A more detailed summary of the formulation can be found in Appendix 3 and is available upon request from the OCPB reviewer or the Division of Pharmaceutical Evaluation 3 (OCPB, DPE 3).

Drug Product:

clindamycin phosphate to the desired site of action (i.e., the vagina) for the local treatment of bacterial vaginosis. The clindamycin phosphate vaginal ovules/suppositories are being manufactured at one strength – 100 mg (expressed as clindamycin base equivalents). The ingredients of the to be marketed ovule formulation are given in the table below.

Component	Amount per Suppository	Amount in Representative Production Batch

Formulations Used in Clinical Studies:

[redacted]

COMMENTS:

There are no formulation issues.

IV. RECOMMENDATION

Item 6 (Human Pharmacokinetics and Bioavailability) of NDA 50-767 for CLEOCIN® Vaginal Ovule (clindamycin phosphate vaginal suppository) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been deemed to be acceptable. There are no comments for the sponsor, other than labeling comments.

V. LABELING COMMENTS FOR THE SPONSOR

See attached Appendix 1, Proposed Labeling, for comments.

VI. GENERAL COMMENTS NOT TO BE SENT TO SPONSOR

1. The sponsor noted that the apparently higher extent and more rapid rate of systemic absorption of clindamycin from intravaginal administration of the ovule, and not the cream, was an unexpected finding. The cream formulation contains already dissolved drug, but the ovule is a solid suppository dosage form [redacted] It was therefore expected that drug absorption would be lower for the suppository than the cream, due to the necessity that drug be in solution prior to absorption. In order to justify the finding of higher systemic drug absorption from the ovule, the sponsor proposed some possible explanations.

   The first was that, in addition to a more rapid release and dissolution of the ovule *in vivo*, it might also be possible that the residence time of the clindamycin suppository in the vagina may be longer than that of the cream. This would result in greater contact time with the vaginal mucosa and a higher drug concentration in the mucosa, which in turn may have facilitated passage of drug into the systemic circulation.

   This hypothesis could not be confirmed within the scope of the present study.

   The second was related to drug or dosage form effects on the vaginal membrane such that the clindamycin phosphate ovule may cause mild vaginal irritation, which may then facilitate drug passage into the systemic circulation. There were 4/12 subjects in the present study (**Subjects 5, 6, 7, 8**) who reported mild to moderate vaginal burning and/or vulvar pruritis after receipt of the ovule, whereas no subjects reported this adverse event after taking the cream. However, serum drug concentrations and serum PK parameters (i.e., AUC and Cmax) following ovule administration were elevated above the mean values for the group in only 2 of these 4 subjects (**Subjects 5 and 7**), while the other 2 subjects (**Subjects 6 and 8**) did not show any trend of enhanced systemic absorption.

   Thus, these findings merely suggest, but do not conclusively demonstrate a local effect of the ovule on the vaginal mucosa/membrane that may result in enhanced systemic absorption of clindamycin in humans.

/S/ 8/9/99

Philip M. Colangelo, PharmD., Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

RD/FT signed by Funmi Ajayi, Ph.D (TL) _____ /S/ 8/9/99

Briefing Attendees (8/3/99): J. Lazor, A. Selen, F. Ajayi, D. Bashaw, F. Pelsor, K. Uhl

cc:
Div. File (HFD-590): NDA 50-767
HFD-590 (J. Winfield, MO)
HFD-590 (C. Chi, PM/CSO)
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10 pages of revised draft labeling have been redacted from this portion of the document.

APPENDIX 2:

REVIEW OF PK ABOSRPTION/BIOAVAILABILITY

STUDY M/1114/0003

Protocol M/1114/0003: **Bioavailability of Clindamycin in Healthy Females Following Administration of Either the Clindamycin Phosphate Vaginal Ovule or Vaginal Cream**

Study dates 1/17/96-3/15/96

NDA Vol. 1.23, p 38 (Technical Report 7215-96-047)

Objectives:
Primary objective – evaluate absolute bioavailability (BA) of the vaginal ovule by comparison to a reference treatment with intravenous clindamycin phosphate. Secondary objective – assess relative BA of the ovule compared to the approved and marketed clindamycin vaginal cream 2%.

Formulations/Treatments:
Treatment A: **Clindamycin Phosphate Vaginal Ovule 100 mg**

Treatment B: **Clindamycin Phosphate Vaginal Cream 2% (100 mg/5 g)**

Treatment C: **Clindamycin Phosphate Sterile IV Solution (10 mg/mL)**

Subjects:
12 healthy females, mean age (range) 31.4 (22-39) yr., mean weight (range) 65.2 (47.2-88.9) kg

Study Design and Methods:
Open label, randomized, three-treatment, two-way crossover design. All 12 female subjects were administered 100 mg doses of the clindamycin vaginal ovule (Treatment **A**) and vaginal cream (Treatment **B**) intravaginally in the evening for 3 consecutive days in crossover fashion. In the third treatment arm, the subjects received an IV infusion of a single 100 mg dose of clindamycin phosphate over 4 minutes in non-crossover fashion (Treatment **C**). Treatments **A** and **B** were administered by each study subject in the presence of a study nurse to ensure proper intravaginal administration of the ovule and cream. Subjects remained in supine position following intravaginal administration of treatments **A** and **B**. There was a minimum washout period of 14 days between each treatment.

> ***NOTE: The IV clindamycin dose of 100 mg used in this study is sub-therapeutic. The recommended adult IV doses range from 600-2700 mg/day in 2, 3, or 4 divided doses.***

Serum was obtained from blood samples collected at predose (0 hr) on study Days 1, 2, and 3, and serially after the 3rd dose on Day 3 from 1 to 72 hrs postdose for intravaginal treatments **A** and **B**. For treatment **C** (IV clindamycin), serum was obtained from serial blood samples collected at pre-infusion (0 hr), and from 0.067 (4 min) to 16 hrs post-infusion.

Safety was assessed via routine laboratory tests, vital signs, and documenting any adverse events reported by the subjects during and upon completion of the study.

Analytical Methods:

Data Analysis:

The pharmacokinetic (PK) parameters were determined [redacted] for the intravaginal formulations and the IV administration. Absolute bioavailability (F) of the intravaginal ovule and cream formulations was estimated as $AUC(0\text{-}24)_{Day\ 3}$ / $AUC(0\text{-}inf)_{iv}$.

Differences in mean serum concentrations at each sampling time and PK parameters between the intravaginal ovule (A) vs. the intravaginal cream (B) were tested for significance using an ANOVA model, with statistical significance defined as $p < 0.05$.

PK Results:

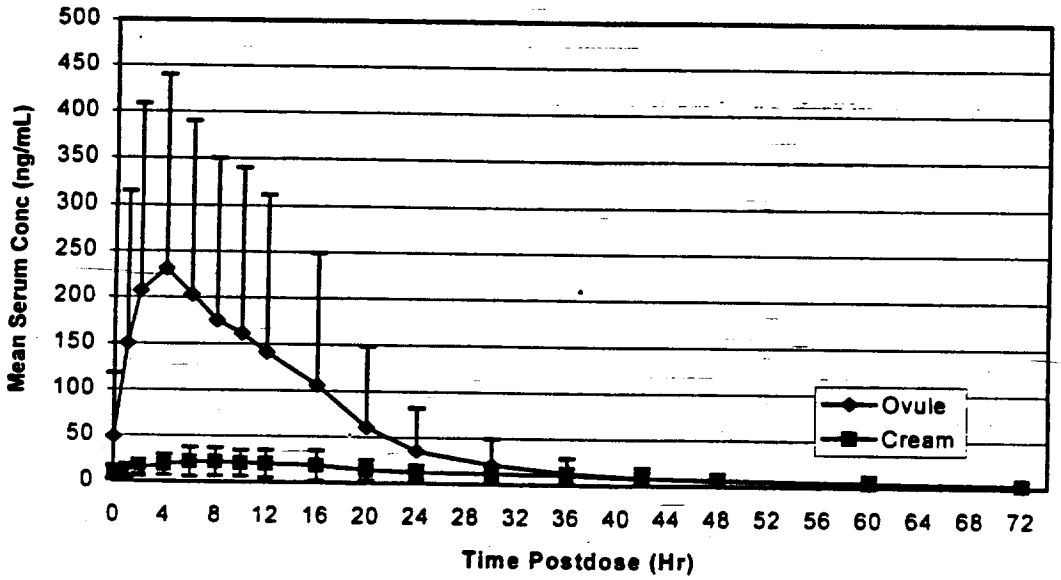
PK data was obtained from all 12 subjects administered the two intravaginal treatments in crossover fashion. One subject (# 9) was dropped from the study after she had a positive pregnancy test prior to entry into the IV treatment arm but after receiving both the clindamycin vaginal ovule and vaginal cream. Thus, PK data following the IV treatment was obtained from 11 subjects.

The mean serum clindamycin concentration-time profiles for the three treatments are illustrated in the two figures below and the mean (SD) serum concentration values from predose (0 hr) to 24 hr after the 3rd intravaginal doses of the ovule and cream are listed in Table 1 at the end of this review.

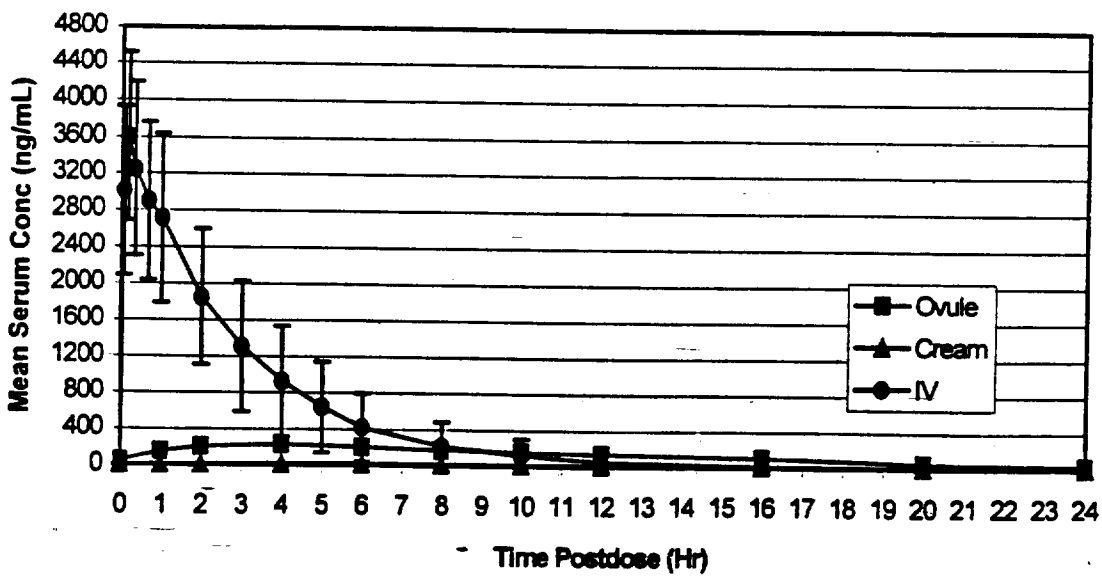
Mean serum clindamycin concentrations following both intravaginal ovule and cream treatments were quantifiable [redacted] just prior to the 3rd dose on Day 3 and remained above 1 ng/mL in the majority of subjects (i.e., 8/12 and 7/12, respectively) at 72 hrs after the 3rd dose. Comparison of the mean serum clindamycin concentrations for the vaginal treatments at each time point showed that drug levels were significantly higher following administration of the vaginal ovule than those for the cream from the time of the 3rd dose on Day 3 through 16 hr postdose ($p < 0.05$). At 24 hrs after the 3rd dose, mean (SD) serum drug concentrations for the ovule vs. cream were 35 ± 46 ng/mL vs. 12 ± 8 ng/mL, respectively ($p = 0.0982$). The inter-subject variability in the mean serum clindamycin concentrations was also substantially higher for the ovule (i.e., %RSD 90-146%) than that of the cream (i.e., %RSD 61-89%).

Visual inspection of the mean concentration-time profiles for all three treatments indicated that mean serum drug levels were substantially higher out to ~6 hrs after a single sub-therapeutic 100 mg clindamycin phosphate dose IV as compared to either the vaginal ovule or vaginal cream treatments.

Mean (SD) Serum Clindamycin Concentrations Following QD Administration of 100 mg Clindamycin Phosphate Vaginal Ovule or Vaginal Cream for 3 Days (N = 12)



Mean (SD) Clindamycin Serum Concentrations Following Single 100 mg IV Dose (N = 11) and After 100 mg QD Vaginal Ovule or Cream for 3 Days (N = 12)



The mean serum PK parameters for the intravaginal ovule and cream treatments and the single IV dose are summarized in the tables below.

Serum Clindamycin Pharmacokinetic Parameters on Day 3 Following Intravaginal Administration of 100mg Doses of Either Clindamycin Phosphate Vaginal Ovule or Cream QD for 3 Days (N = 12)

Parameter	Vaginal Ovule (Treatment A)		Vaginal Cream (Treatment B)		p-value
	Mean ± SD (% RSD)	Range	Mean ± SD (% RSD)	Range	
$AUC_{0\text{-}24}$ (ng.h/mL)	3182 ± 3081 (97%)		417 ± 282 (68%)		.0044
Cmax (ng/mL)	270 ± 244 (90%)		23.8 ± 15.9 (67%)		.0039
Tmax (h)	4.6 ± 2.6 (56%)		8.0 ± 4.0 (50%)		.0701
λz (h^{-1})	0.062 ± 0.043 (69%)		0.048 ± 0.023 (48%)		.1317
T½ (h)*	11.2		14.4		NC
F_{abs} (%)**	30.5 ± 21.4 (70%)		4.26 ± 3.66 (86%)		.0004
F_{Cmax}(%)***	7.91 ± 6.88 (87%)		0.633 ± 0.448 (68%)		.0047

* Harmonic mean
NC = Not Calculated
** Absolute bioavailability calculated as Day 3 AUC(0-24)vag/AUC(0-∞)iv; N = 11
*** N=11

Serum Clindamycin Pharmacokinetic Parameters Following Intravenous Administration of a Single 100mg Dose of Clindamycin Phosphate (N = 11)

Parameter	Mean ± SD (% RSD)	Range
$AUC_{0\text{-}t6}$ (ng.hr/mL)	10,600 ± 5450 (51%)	
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	10,600 ± 5630 (53%)	
Cmax (ng/mL)	3720 ± 910 (24%)	
Tmax (h)	0.22 ± 0.16 (73%)	
λz (h^{-1})	0.403 ± 0.079 (20%)	
T½ (h)*	1.72	
Vss (L)	26.8 ± 6.61 (25%)	
CL (L/h)	11.2 ± 4.18 (37%)	

* Harmonic mean

The PK results indicated that overall systemic exposure to clindamycin was substantially greater for the ovule (**Treatment A**) than the cream (**Treatment B**) after 3 consecutive days of 100 mg doses of each formulation. Mean clindamycin AUC(0-24), Cmax, Fabs, and FCmax values on Day 3 were significantly higher for the vaginal ovule than for the vaginal cream ($p < 0.05$ for all parameters). The mean AUC(0-24) and Cmax estimates for the ovule were ~8-times and ~11-times higher, respectively, than those for the cream. Although not statistically significant, the mean Tmax for the ovule was shorter by nearly one-half of that for the cream. The mean absolute bioavailability (Fabs) compared to IV administration for the ovule was 30% versus 4% for the cream ($p = 0.0004$). Thus, systemic absorption was approximately 7-fold greater after intravaginal administration of the ovule compared to the vaginal cream.

Although the inter-subject variability in the mean PK parameters was substantial for both intravaginal treatments (i.e., %RSD values >50% for all parameters), it was especially pronounced for the ovule with %RSD values ranging from ~60-100%. Individual AUC(0-24) values for the ovule varied 27-fold over a range from and Cmax values for the ovule varied 25-fold over a range from For the cream, the individual values of AUC(0-24) and Cmax varied to a lesser extent, i.e., 9-fold.

The systemic absorption/PK of clindamycin from the vaginal cream determined in the healthy females in this study was consistent with that reported by the sponsor in previous bioavailability studies and in the approved labeling for the vaginal cream in both healthy subjects and patients with bacterial vaginosis.

The variability in the mean estimates of absolute bioavailability (Fabs) was substantial for both intravaginal treatments. For the ovule, the individual estimates of Fabs varied 11-fold over a range from 6.5 to 70%, and varied 9-fold for the cream from 1.6 to 15%. For the ovule, 4/11 subjects had Fabs estimates greater than 40%, i.e., ranging from 44 to 70%, while another 4/11 subjects had Fabs values below 20%, i.e., ranging from 6.5 to 16.5%. For the cream, 10/11 subjects had Fabs estimates below 10% (range 1.6 to 6.4%), and for one subject, Fabs was above 10% (i.e., 14.5%).

Systemic exposure to clindamycin was substantially higher following single IV administration of a sub-therapeutic dose of clindamycin phosphate (**Treatment C**). The mean AUC(0-inf) following the single 100 mg IV dose was ~3-times than that of the ovule and ~25-times that of the cream, while the mean Cmax for the IV dose was ~14-times that for the ovule and ~150-times that for the cream.

Subject #12 had either the highest or nearly the highest extent of overall systemic exposure to clindamycin after all three treatments (i.e., vaginal **Treatments A and B**; IV **Treatment C**). The AUC estimates for this subject were substantially greater than the mean values for each of the 3 treatment groups, i.e., 4-times the ovule at 11,423 ng.hr/mL; 1.5-times the cream at 634 ng.hr/mL; 2.5-times the IV at 25,500 ng.hr/mL. The values for Cmax in this subject also showed a similar trend, with values that were 2.5-times (at 666 ng/mL), 1.2-times (at 29 ng/mL), and 1.3-times (at 4740 ng/mL) the mean Cmax estimates for **Treatments A, B, and C**, respectively. A reason for the higher than average drug exposure in this subject appeared to be reduced drug elimination, as evidenced by the prolonged estimates of the apparent T½ for the ovule (22 hrs) and cream (30 hrs), and the lowest systemic clearance (CL = 3.9 L/hr) / most prolonged T½ (3.0 hrs) after IV clindamycin administration.

Despite the greater extent of systemic drug exposure after treatment with the vaginal ovule, vaginal cream, and IV clindamycin, Subject #12 completed all three treatments. Three adverse events of mild severity were reported with treatment with the ovule and were considered NOT to be related to treatment (i.e., eczema, nasal discharge, and cough). No adverse events were reported with the vaginal cream or IV treatments for this subject. A noteworthy finding on screening was that Subject #12 was judged to have an abnormal pelvic exam due to a past history of hysterectomy. It is not known whether this may have also contributed to the higher degree of systemic drug exposure.

Adverse Events (AE's):
A total of 56 non-serious adverse events were reported by 11 of the 13 subjects enrolled in the study. Twenty-eight (28) of the 56 total adverse events were considered to be possibly related to investigational medication. All of the reported events were considered to be mild, except for one headache, which was reported as moderate. No adverse events were reported as severe.

The greatest number adverse events were reported following administration of the vaginal ovule (38 events by 10 subjects) compared to the vaginal cream (17 events by 8 subjects) and the IV treatment (1 event by 1 subject). Gastrointestinal disturbances were the most commonly reported AE, occurring in 6 subjects receiving the ovule, 4 subjects receiving the cream, and none with the IV treatment. Headache was also a frequently reported event, which occurred in 3 subjects during ovule treatment, 5 subjects during vaginal cream treatment, and 1 subject during IV treatment. A sensation of vaginal burning was reported by 3 subjects (**Subject #'s 5, 6, 8**), and vulvar or vaginal pruritis was reported by 2 subjects (**Subject #'s 5 and 7**) during treatment with the vaginal ovule. These vaginal AE's were not reported by any subject during treatment with either the vaginal cream or the intravenous infusion of clindamycin.

> *Overall, although administration of the vaginal ovule and vaginal cream for 3 consecutive days appeared to be well tolerated, there were more AE's associated with administration of the vaginal ovule. In particular, there were treatment associated vaginal AE's (burning and/or pruritis) that occurred only with the ovule (4/12 subjects) but not with the vaginal cream.*

Comparison of Systemic Exposure/Systemic Absorption with Oral and IV Clindamycin Formulations:
Clindamycin is marketed for systemic administration as capsules for oral use and as a sterile intravenous (IV) solution for parenteral use. The recommended oral dose regimen is 150 to 450 mg Q6 hrs (600-1800 mg/day) and the IV dose regimen is 600 to 2700 mg/day in 2, 3, or 4 divided doses.

Mean AUC estimates reported in previously conducted studies, provided by the sponsor in this NDA submission, with **oral clindamycin capsules** after single and multiple doses in healthy adult subjects ranged from [redacted] mean Cmax values in these studies ranged from [redacted] Based on the mean AUC estimate determined after 3 consecutive days of intravaginal dosing with the 100 mg clindamycin phosphate ovule in the present NDA study, systemic exposure to clindamycin from the vaginal ovule is lower than that from oral capsule administration by a factor of 2 to 18. The Cmax with the ovule is lower than that of the oral capsule by a factor of 7 to 17.

In the approved labeling for **clindamycin phosphate IV solution**, average Cmax values of ~11000 to ~14000 ng/mL were reported after multiple dose administration of 600 mg Q8 hr (1800 mg/day), 600 mg Q6 hr (2400 mg/day), and 900 mg Q8 hr (2700 mg/day). These peak concentrations are ~40- to ~50-times the mean Cmax observed after 3 consecutive days of intravaginal dosing with the 100 mg clindamycin phosphate ovule in the present NDA study.

> *These PK comparisons indicate that overall systemic exposure to clindamycin from the ovule is considerably lower than that from recommended oral and IV doses. Based on this, it is expected that intravaginal administration of the ovule would not cause any additional safety concerns, **with respect to systemic adverse events**, over those that have already been identified and reported with systemic administration of clindamycin.*

Conclusions:

Overall, the PK results suggested that both the rate (i.e., based on Cmax and Tmax) and extent (i.e., based on AUC) of systemic absorption from intravaginal administration of the clindamycin phosphate vaginal ovule was greater than that from the vaginal cream. Intravaginal administration of the clindamycin phosphate vaginal ovule at the proposed dosage regimen for treatment of bacterial vaginosis, i.e., 100 mg ovule for 3 consecutive days, resulted in significantly higher systemic absorption/systemic drug exposure than that following the same dosage regimen with the vaginal cream in healthy female subjects. The mean bioavailability (F) of the ovule, as compared to a single ***sub-therapeutic*** 100 mg dose of IV clindamycin phosphate, was significantly greater at 30% versus 4% for the cream ($p = 0.0004$). Thus, systemic absorption was approximately 7-fold greater after intravaginal administration of the ovule compared to the vaginal cream.

> *The systemic absorption/PK of clindamycin from the clindamycin phosphate vaginal cream determined in the healthy females in this study was consistent with that reported by the sponsor in previous bioavailability studies and in the approved labeling for the vaginal cream in both healthy subjects and patients with bacterial vaginosis.*

The between subject variability in the estimates of AUC, Cmax, and F was substantial for both intravaginal treatments, with %RSD values ranging from ~70 to ~100%. Individual AUC(0-24) values for the ovule varied 27-fold over a range from [redacted] and Cmax values for the ovule varied 25-fold over a range from [redacted] For the cream, the individual values of AUC(0-24) and Cmax varied to a lesser extent, i.e., 9-fold. Estimates of F for the ovule varied 11-fold over a range from 6.5 up to 70%; and varied 9-fold for the cream from 1.6 up to 15%.

Despite the increased systemic absorption observed with the vaginal ovule, systemic exposure to clindamycin was still substantially higher following single IV administration of a ***sub-therapeutic dose*** of clindamycin phosphate (**Treatment C**). The mean AUC following the single 100 mg IV dose was ~3-times than that of the ovule, while the mean Cmax for the IV dose was ~14-times that for the ovule. The mean AUC and Cmax following the IV clindamycin dose was ~25-times and ~150-times, respectively, to that of the vaginal cream.

All reported adverse events (AE's) with the ovule were considered to be either mild or moderate and no adverse events were reported as severe. Although administration of the both vaginal ovule and vaginal cream for 3 consecutive days appeared to be well tolerated by all subjects, there were more AE's associated with administration of the vaginal ovule. In particular, there were treatment associated vaginal AE's (burning and/or pruritis) that occurred only with the ovule (4/12 subjects) but not with the vaginal cream.

Pharmacokinetic (PK) comparisons indicated that overall systemic exposure to clindamycin from the vaginal ovule is considerably lower than that from recommended oral (i.e., ~2-20-times lower) and IV (i.e., ~40-50-times lower) doses. *Based on this and the results from this present study, it is expected that intravaginal administration of the ovule would not cause any additional safety concerns, **with respect to systemic adverse events**, over those that have already been identified and reported with systemic administration of clindamycin.*

General Comments:

The sponsor noted that the apparently higher extent and more rapid rate of systemic absorption of clindamycin from intravaginal administration of the ovule, and not the cream, was an unexpected finding. The cream formulation contains already dissolved drug, but the ovule is a solid suppository dosage form that contains milled, not dissolved, drug. It was therefore expected that drug absorption would be lower for the suppository than the cream, due to the necessity that drug be in solution prior to absorption. In order to justify the finding of higher systemic drug absorption from the ovule, the sponsor proposed some possible explanations.

The first was that, in addition to a more rapid release and dissolution of the ovule *in vivo*, it might also be possible that the residence time of the clindamycin suppository in the vagina may be longer than that of the cream. This would result in greater contact time with the vaginal mucosa and a higher drug concentration in the mucosa, which in turn may have facilitated passage of drug into the systemic circulation.

This hypothesis could not be confirmed within the scope of the present study.

The second was related to drug or dosage form effects on the vaginal membrane such that the clindamycin phosphate ovule may cause mild vaginal irritation, which may then facilitate drug passage into the systemic circulation. There were 4 subjects in the present study (**Subject #'s 5, 6, 7, 8**) who reported vaginal burning and/or vulvar pruritis after receipt of the ovule, whereas no subjects reported this adverse event after taking the cream. However, serum drug concentrations and serum PK parameters (i.e., AUC and Cmax) following ovule administration were elevated above the mean values for the group in only 2 of these 4 subjects (**Subjects 5 and 7**), while the other 2 subjects (**Subjects 6 and 8**) did not show any trend of enhanced systemic absorption.

Thus, these findings merely suggest, but do not conclusively demonstrate a local effect of the ovule on the vaginal mucosa/membrane that results in enhanced systemic absorption of clindamycin in humans.

Labeling:

*Agree with all labeling statements, **except** under **OVERDOSAGE (2nd Sentence)**:*

Dosing with three CLEOCIN Vaginal Ovules concurrently would result in systemic exposure approximating that of a single therapeutic oral or parenteral dose (see ADVERSE REACTIONS).

*There was **no** evidence or **no** other predictions/extrapolations provided in the current study (M/1114/0003) regarding the **concurrent** administration of 3 vaginal ovules, i.e., **inserting all 3 ovules at once intravaginally**.*

Recommend deleting this 2nd sentence.

Table 1. Serum Clindamycin Concentrations (ng/mL) on Day 3 Following Administration of 100-mg Doses of Either Clindamycin Phosphate Vaginal Cream or Vaginal Ovule Once Daily for 3 Days (n=12)

Time Postdose (hr)	Clindamycin Phosphate Vaginal Ovule (Treatment A)		Clindamycin Phosphate Vaginal Cream (Treatment B)		p-value
	Mean ± SD	Range	Mean ± SD	Range	
0	48.2 ± 69.3		9.91 ± 7.12		.0463
1	150 ± 164		11.4 ± 7.36		.0195
2	207 ± 201		14.6 ± 9.14		.0079
4	231 ± 209		18.4 ± 11.2		.0025
6	203 ± 187		21.7 ± 15.9		.0019
8	175 ± 175		21.7 ± 15.1		.0043
10	161 ± 179		20.6 ± 13.9		.0094
12	141 ± 170		20.0 ± 14.9		.0188
16	106 ± 143		18.4 ± 16.4		.0446
20	60.4 ± 87.9		14.1 ± 11.1		.0824
24	35.2 ± 46.6		12.1 ± 7.94		.0982

2 *pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.*