CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050680/S002

MICROBIOLOGY REVIEW(S)

Ch:
590

DEC 8 1997

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 50-680

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	28-AUG-97
CDER RECEIPT DATE:	02-SEP-97
REVIEW ASSIGN DATE:	18-SEP-97
REVIEW COMPLETE DATE:	23-OCT-97

SPONSOR: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

CONTACT PERSON: Donald R. Gieseker, Pharm. D.
Associate Director, U. S. Regulatory Affairs
Phone Number: (616) 833-8527

SUBMISSION REVIEWED: Amendment to Supplement SE2-002

DRUG CATEGORY: Antimicrobial: Clindamycin

INDICATIONS: Bacterial Vaginosis

DOSAGE FORM: Vaginal Cream

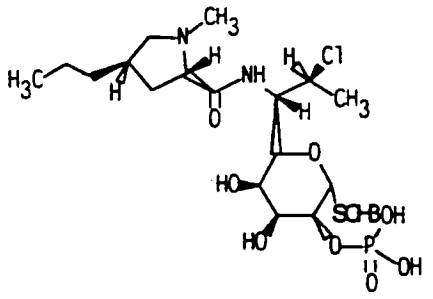
DRUG PRODUCT NAME

PROPRIETARY: Cleocin® Vaginal Cream

NONPROPRIETARY/USAN: Clindamycin phosphate vaginal cream

CHEMICAL NAME: L-threo-alpha-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-meth yl -4- propyl - 2-pyrrolidinyl)-carbonyl]amino]-1-thio, 2-(dihydrogen phosphate), (2S-trans)-

STRUCTURAL FORMULA:



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

Molecular Weight: 504.97

SUPPORTING DOCUMENTS:

IND:
NDA: 50,441--Cleocin phosphate solution
NDA: 50,537--Cleocin topical solution
NDA: 50-600--Cleocin -T-topical solution
NDA: 50-615--Cleocin-T-Gel

BACKGROUND:

This amendment is a response to a not-approvable letter dated May 7, 1996. The submission contains the results of a clinical trial conducted in Europe comparing the efficacy and safety of a 3-day course versus a 7-day course of 2% clindamycin vaginal cream in the treatment of bacterial vaginosis.

Five hundred and eighty-one women who met the criteria for bacterial vaginosis (BV) (vaginal fluid pH>4.5; "fishy" vaginal fluid odor after addition of 10% KOH; presence of clue cells; increased thin, homogenous, malodorous vaginal discharge) were randomized to receive treatment with clindamycin vaginal cream, either for 3 days (288 patients) or 7 days (293 patients) in a multicenter, double-blind study. The primary objective was to determine whether the two regimens are therapeutically equivalent. A secondary objective was to compare the safety and efficacy of the two regimens in the prevention of recurrence after initial cure.

Patients were supposed to have a pretreatment evaluation and three follow-up visits on Day 10, Day 30, and Day 90 after the start of treatment to assess resolution and onset of recurrence.

Records of 47 randomized patients (27 patients in the 3-day group and 20 in the 7-day group) showed no evidence that the drug was received. These patients were not included in the study. The data was assessed according to the presence/absence of the four diagnostic criteria for bacterial vaginosis (vaginal fluid pH >4.5; "fishy" amine odor; clue cells, and increased characteristic vaginal discharge). Cure was defined as the resolution of all four criteria and improvement as the resolution of any three criteria. Another analysis was performed based on FDA recommendations that only amine odor and clue cells be used as diagnostic criteria.

The precise etiology of bacterial vaginosis is not known. It appears that the cause is an overgrowth of both aerobic and anaerobic vaginal bacterial flora. The most common anaerobes involved appear to be members of the *Bacteroides* and *Peptococcus* species. Changes in the prevalence of lactobacillus in the vagina also takes place. Routine cultures are not usually useful, either in establishing the diagnosis or following treatment efficacy. No cultures were performed in the submitted study. Clindamycin is active against *Bacteroides* species and *Peptococcus* species.

This study is an attempt to show that a 3-day treatment course is as effective as a 7-day treatment course and that the incidence of recurrence is the same for both treatments.

Tests for the presence of *Candida albicans*, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae* were performed at the pretreatment visit. Patients with evidence of infection with these organisms were removed from the study. Table 1 shows the organisms isolated pretreatment. Since patients were removed from the study and were, therefore, not evaluable if these organisms were detected, none of these organisms were seen in the evaluable patients. In the intent to treat (ITT) patients *Candida albicans* was detected pretreatment in 16 patients (9 in the 3-day group and 7 in the 7-day group) and *Chlamydia trachomatis* was seen in 12 patients (9 in the 3-day group and 3 in the 7-day group). *Neisseria gonorrhoeae* was detected in only two patients one in each group.

APPEARS THIS WAY
ON ORIGINAL

TABLE 1
Organisms Isolated Pretreatment

Patient Subset	Organism	CVC* 3-Day				CVC* 7-Day				Total			
		Sampled		Positive		Sampled		Positive		Sampled		Positive	
		n	%	n	%	n	%	n	%	n	%	n	%
Evaluable Patients	*Trichomonas vaginalis*	213	100	0	0.0	235	100	0	0.0	448	100	0	0.0
	Candida albicans	213	100	0	0.0	235	100	0	0.0	448	100	0	0.0
	Neisseria gonorrhoeae	211	99.1	0	0.0	234	99.6	0	0.0	445	99.3	0	0.0
	Chlamydia trachomatis	211	99.1	0	0.0	233	99.1	0	0.0	444	99.1	0	0.0
ITT Patients	*Trichomonas vaginalis*	261	100	0	0.0	273	100	0	0.0	534	100	0	0.0
	Candida albicans	261	100	9	3.4	273	100	7	2.6	534	100	16	3.0
	Neisseria gonorrhoeae	258	98.9	1	0.4	271	99.3	1	0.4	529	99.1	2	0.4
	Chlamydia trachomatis	258	98.9	9	3.5	271	99.3	3	1.1	529	99.1	12	2.3

* CVC = Clindamycin Vaginal Cream Treatment

At each follow-up visit tests were performed to detect *Candida albicans* or *Trichomonas vaginalis*. TABLE 2 shows the organisms isolated posttreatment. In the evaluable patients sampled, *Trichomonas vaginalis* was detected in one patient in the 7-day treatment group at Day 10 and two patients in the 3-day treatment group at Day 30. *Candida albicans* was detected more often. The incidence was similar between the two groups. In the 3-day treatment group, *C. albicans* was found in 8 patients (3.6% of those sampled) at Day 10, 19 (10.5%) at Day 30, and 14 (8.9%) at Day 90, compared to 11 (4.4%), 16 (7.9%), and 20 (11.3%) for the same visits, respectively, for patients in the 7-day group. In the intent to treat (ITT) population the number of patients testing positive for *T. vaginalis* was the same as for the evaluable patients at all three follow-up visits for both treatment groups. *C. albicans* was more frequently isolated than *T. vaginalis*. In the 3-day treatment group, *C. albicans* was cultured or seen on a vaginal smear for 14 patients (5.6% of those sampled) at Day 10, 21 (10.3%) at Day 30, and 19 (10.4%) at Day 90, compared to 12 (4.5%), 18 (8.0%), and 22 (11.1%) patients for the same visits, respectively for the 7-day treatment group.

Numerous patients have *Candida albicans* both before and/or after treatment, but the number of patients with this organism is approximately equal for both the 3-day and 7-day treatment groups. It appears that the number of patients with *Candida albicans* may increase in both treatment groups from pretreatment to at least Day 30 posttreatment. This may be due to the fact that treatment has eliminated other organisms and allowed *C. albicans* to grow.

TABLE 2
Organisms Isolated Posttreatment

Patient Subset	Visit	Organism	CVC* 3-Day				CVC* 7-Day				Total			
			Sampled		Positive		Sampled		Positive		Sampled		Positive	
			n	%	n	%	n	%	n	%	n	%	n	%
Evaluable Patients	Day 10	*Trichomonas vaginalis*	224	99.6	0	0.0	251	100	1	0.4	475	99.8	1	0.2
		Candida albicans	224	99.6	8	3.6	251	100	11	4.4	475	99.8	19	4.0
	Day 30	*Trichomonas vaginalis*	181	100	2	1.1	202	100	0	0.0	383	100	2	0.5
		Candida albicans	181	100	19	10.5	202	100	16	7.9	383	100	35	9.1
	Day 90	*Trichomonas vaginalis*	158	100	0	0.0	177	100	0	0.0	335	100	0	0.0
		Candida albicans	158	100	14	8.9	177	100	20	11.3	335	100	34	10.1
ITT Patients	Day 10	*Trichomonas vaginalis*	251	96.2	0	0.0	266	97.4	1	0.4	517	96.8	1	0.2
		Candida albicans	251	96.2	14	5.6	266	97.4	12	4.5	517	96.8	26	5.0
	Day 30	*Trichomonas vaginalis*	204	100	2	1.0	225	100	0	0.0	429	100	2	0.5
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	Day 90	*Trichomonas vaginalis*	182	100	0	0.0	199	100	0	0.0	381	100	0	0.0
		Candida albicans	182	100	19	10.4	199	100	22	11.1	381	100	41	10.8

CVC = Clindamycin Vaginal Cream Treatment

CONCLUSIONS & RECOMMENDATIONS:

Routine cultures are not used to establish a diagnosis or follow treatment efficacy. Bacteriological outcome is, therefore, not involved in this study. No microbiological conclusions about efficacy can be made. It appears that very few patients have *Trichomonas vaginalis* before or after treatment. Numerous patients have *Candida albicans* both before and/or after treatment, but the number of patients with this organism is approximately equal for both the 3-day and 7-day treatment groups. It appears that the number of patients with *Candida albicans* may increase in both treatment groups from pretreatment to at least Day 30 posttreatment. This may be due to the fact that treatment has eliminated other organisms and allowed *C. albicans* to grow. Both treatment groups appear equal as far as detected vaginal pathogens pre- and posttreatment are concerned.

Recommendation

From the microbiological viewpoint this supplement should be approved. Since bacteriological outcome is not involved in this study no microbiological conclusion can be made. Both treatment groups appear equal as far as detected vaginal pathogens pre- and posttreatment are concerned.

APPEARS THIS WAY
ON ORIGINAL

/S/

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir /S/ Signature 12/8/97 Date
HFD-590/TLMicro /S/ Signature 11/12/97 Date

CC:

HFD-590/Original NDA # 50-680
HFD-590/Division File
HFD-590/TLMicro/LUtrup
HFD-590/Micro/PDionne
HFD-590/MO/DDavis
HFD-590/Pharm/KHastings
HFD-590/CSO/CChi
HFD-590/Chem/NSchmuff

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NOV 1 2 1997

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CONTACT PERSON: Donald R. Gieseker, Pharm. D.
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Phone Number: (616) 833-8527

SUBMISSION REVIEWED: Amendment to Supplement SE2-002

DRUG CATEGORY: Antimicrobial: Clindamycin

INDICATIONS: Bacterial Vaginosis

DOSAGE FORM: Vaginal Cream

DRUG PRODUCT NAME

PROPRIETARY: Cleocin® Vaginal Cream
NONPROPRIETARY/USAN: Clindamycin phosphate vaginal cream
CHEMICAL NAME: L-threo-alpha-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-meth yl -4- propyl - 2-pyrrolidinyl)-carbonyl]amino]-1-thio, 2-(dihydrogen phosphate), (2S-trans)-
STRUCTURAL FORMULA:

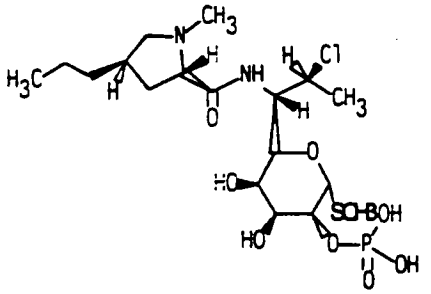

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TABLE 2
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CVC = Clindamycin Vaginal Cream Treatment

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

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Recommendation

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APPEARS THIS WAY
ON ORIGINAL

/S/

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir /S/ Signature 12/5/97 Date
HFD-590/TLMicro /S/ Signature 11/12/97 Date

CC:

HFD-590/Original NDA # 50-680
HFD-590/Division File
HFD-590/TLMicro/LUtrup
HFD-590/Micro/PDionne
HFD-590/MO/DDavis
HFD-590/Pharm/KHastings
HFD-590/CSO/CChi
HFD-590/Chem/NSchmuff

APPEARS THIS WAY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 050680/S002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 50,680/ S-002 **Submission Date:** December 17,1997

Cleocin[R] Vaginal Cream (Clindamycin Phosphate)

The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

Reviewer: Funmilayo O. Ajayi, Ph.D.

Type of Submission: NDA Supplement

Synopsis: The above was submitted for approval for the treatment of bacterial vaginosis using a 3 day regimen. The Biopharmaceutics section of this NDA was reviewed by Dr. Frank Pelsor. Hence, this is a memo to convey the labeling changes.

Labeling Comments: Please refer to the attached e-mail from Dr. Frank Pelsor. Hence, the Clinical Pharmacology section of the package insert should read as follows:

Following a once a day intravaginal dose of 100 mg of Clindamycin phosphate vaginal cream 2%, administered to 6 healthy female volunteers for 7 days, approximately 5% ( ) of the administered doe was absorbed systemically. The peak serum Clindamycin concentration observed on the first day averaged 18 ng/mL and averaged 25 ng/mL on day 7. These peak concentrations were attained approximately 10 hours post dosing

Following a once a day intravaginal dose of 100 mg of Clindamycin phosphate vaginal cream 2%, administered for 7 days to 5 women with bacterial vaginosis, absorption was slower and less variable than that observed in healthy females. Approximately 5% ( ) of the dose was absorbed systemically. The peak serum Clindamycin concentration observed on the first day averaged 13 ng/mL and averaged 16 ng/mL on day 7. These peak concentrations were attained approximately 14 hours post dosing

There was little or no systemic accumulation of Clindamycin after repeated vaginal dosing of Clindamycin phosphate vaginal cream 2%. The systemic half-life ~~t1/2~~ was

2/27/98

Funmilayo O. Ajayi, Ph.D.
Division of Pharmaceutical Evaluation III

cc: NDA 50-680, HFD-590 (Clinical Division)
HFD-880 (DPE3,Pelsor,Ajayi)
CDR (Attn: B. Murphy)

DEC 1 5 1996

NDA 50-680
Clindamycin phosphate cream 2%
CLEOCIN® 3 VAGINAL CREAM

Submission Date: June 8, 1995

Sponsor: Upjohn Company
Kalamazoo, MI 49001

Reviewer: F. Pelsor

Submission Type: Efficacy Supplement, S-002

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

The purpose of the supplemental application was to request approval for a 3-day dosing regimen of 5 gm clindamycin phosphate cream 2% *qd* for treatment of bacterial vaginosis. The approved regimen is 5 gm clindamycin phosphate cream 2% (CLEOCIN® VAGINAL CREAM) *qd* x 7 days.

The sponsor was issued a not approvable letter (dated May 7, 1996) because the FDA analysis of the clinical study data showed that the 3-day regimen was statistically inferior to the 7-day regimen.

COMMENTS:

1. The Human Pharmacokinetics and Biopharmaceutics Section of the application contains the reference (Borin, MT *et al.*, *Clin Pharmacol Ther*, 51:185, 1992) to a study of clindamycin absorption following intravaginal administration. The study is the source for information provided in the CLINICAL PHARMACOLOGY Section of the approved product label. In this application, the sponsor proposed to decrease the number of daily doses while maintaining the same daily dose.

2. CLEOCIN® 3 VAGINAL CREAM is the same formulation as CLEOCIN® VAGINAL CREAM. However, tubes with a nominal capacity of 21 grams (for 3-day treatment) and 12 grams (product samples) will be added to the 40-gram tube size in the original NDA.

RECOMMENDATIONS:

From a biopharmaceutics standpoint, no further review of supplement 002 to NDA 50-680, is necessary.

/S/ 12/13/96

Francis R. Pelsor, Pharm. D.
Division of Pharmaceutical Evaluation III

JA Lazor, Pharm D for /S/ 12/16/96

FT Initialed by NFleischer, Ph.L.

CC:
NDA 50-680 orig.
HFD-520 (Clinical Division)
HFD-870 (Clarence Bott, PKLN 13B-31)
HFD-880 (DPEIII, Pelsor)
HFD-340 (Vishwanathan)
HFD-520/STrostle

APPEARS THIS WAY
ON ORIGINAL