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RESEARCH**

APPLICATION NUMBER:

50-793

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 50-793

REVIEWER : Kalavati Suvarna
CORRESPONDENCE DATE : 10-30-03
CDER RECEIPT DATE : 10-31-03
REVIEW ASSIGN DATE : 11-05-03
REVIEW COMPLETE DATE : 07-09-04

SPONSOR: KV Pharmaceutical Company
2503 S. Hanley Road
St. Louis, MO 63144.

SUBMISSION REVIEWED: N-000

DRUG CATEGORY: Anti-bacterial

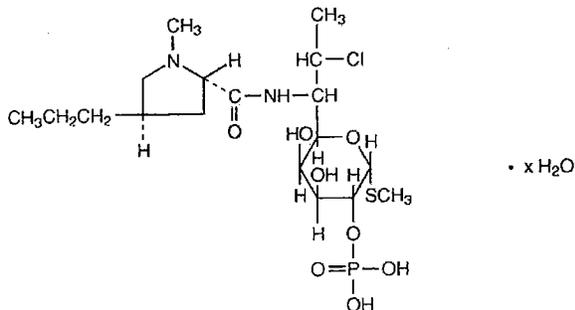
INDICATION: Treatment of bacterial vaginosis

DOSAGE FORM: 2% Vaginal Cream

PRODUCT NAMES:

- a. **PROPRIETARY:** _____
- b. **NONPROPRIETARY:** Clindamycin phosphate
- c. **CHEMICAL:** methyl 7-chloro- 6,7,8-trideoxy-6-(1-methyl- *trans*- 4-propyl-L-2 -pyrrolidinecarboxamido)-1-thio-L- *threo*-(*alpha*)-*D*-galacto- octopyranoside 2-(dihydrogen phosphate).

STRUCTURAL FORMULA:



Molecular weight: 504.97
Empirical Formula: C₁₈H₃₄ClN₂O₈PS

SUPPORTING DOCUMENTS: _____ IND # 62397

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1. EXECUTIVE SUMMARY:

The subject of this NDA is _____, a site release clindamycin phosphate bioadhesive vaginal cream administered as a single dose for the treatment of bacterial vaginosis (BV). The applicant is seeking approval under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act as the drug product contains the same active ingredient (clindamycin phosphate) as the approved reference drug, Cleocin[®] vaginal cream.

The support for the preclinical microbiology aspects of the application is based on published literature and the approved label for Cleocin[®] vaginal cream. _____ and Cleocin, both contain 2% clindamycin phosphate that is hydrolyzed *in vivo* to the active ingredient, clindamycin. *In vitro*, clindamycin is active against most strains of *Gardnerella vaginalis*, *Mycoplasma hominis*, *Bacteroides* sp, *Mobiluncus* sp, and *Peptostreptococcus* sp., which are associated with BV. Clindamycin does exhibit some activity against *Lactobacillus in vitro*. Of the 2 studies that evaluated the effect of clindamycin on vaginal lactobacilli colonization, one study showed a transient decrease at end of therapy while the other did not. Such an effect appeared to be reversed with increased colonization by vaginal lactobacilli at 3 weeks after discontinuation of therapy.

In clinical studies, the efficacy of _____ was similar to Cleocin and superior to placebo in the treatment of bacterial vaginosis. The studies only provided information on the nugent scores using vaginal swabs at baseline and post-treatment. No information was available on the species of bacteria at baseline and post-treatment in patients enrolled in the clinical studies. Therefore, the activity of clindamycin against various organisms associated with BV could not be analyzed in the clinical studies. However, the cure by nugent criteria suggests that there was an increase in *Lactobacillus* morphotypes and decrease in the *Gardnerella*, *Bacteroides* and *Mobiluncus* morphotypes in 55% patients at 21-30 days after discontinuation of treatment with _____

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2. INTRODUCTION AND BACKGROUND:

The subject of this NDA is _____, a site release clindamycin phosphate bioadhesive vaginal cream administered as a single dose for the treatment of bacterial vaginosis (BV). Clindamycin phosphate (2%), the active ingredient of _____ vaginal cream, has been approved as a prescription product (CLEOCIN[®] vaginal cream) for treatment of BV. Besides clindamycin, metronidazole is approved for the treatment of BV.

Bacterial vaginosis is a common vaginal condition seen in reproductive age women. Patients with BV show an increase in vaginal pH, and milky discharge with fishy odor. The etiology of bacterial vaginosis is thought to be due to replacement of the *Lactobacillus* sp in the vagina with high concentrations of anaerobic bacteria (for example, *Prevotella* sp, *Mobiluncus* sp, *Gardnerella vaginalis* and *Mycoplasma hominis*).

Clindamycin phosphate is hydrolyzed *in vivo* to the active compound, clindamycin.

3. PRECLINICAL MICROBIOLOGY:

The sponsor is relying on published literature and the approved label for CLEOCIN[®] vaginal cream, to support the preclinical microbiology section of the label.

3.1. Mechanism of action:

Clindamycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. It affects the peptide chain initiation step in protein synthesis (See CLEOCIN[®] vaginal cream approved label).

3.2. Activity *in vitro*:

In vitro, clindamycin is active against most strains of *Gardnerella vaginalis*, *Mycoplasma hominis*, *Bacteroides* sp, *Mobiluncus* sp, and *Peptostreptococcus* sp., that are associated with BV (See CLEOCIN[®] vaginal cream approved label). However, the approved label does not have information on the activity of clindamycin against *Lactobacillus*.

Activity of clindamycin against *Lactobacillus* in broth and biofilms:

The *in vitro* activity of clindamycin and other antibacterial agents against *Lactobacillus acidophilus* was compared to the activity against *G. vaginalis* using a continuous culture biofilm, tube broth dilution method, and E-test (Muli and Struthers, 1998, AAC, 42: 1428-1432). For the continuous culture biofilm, Sorbarod filters were inoculated with 3 ml of an overnight culture of *G. vaginalis* ATCC 14018 or *L. acidophilus* ATCC 832 strains and incubated at 37°C for 24 hours and feed broth passed through a peristaltic pump. Two feed media [Brain heart infusion (BHI) broth or deMan, Rogosa and Sharp (MRS) broth] were used. The biofilm cultures were then exposed to different concentrations of the drug for 18 hours. The effluent from the biofilm was collected for 15 minutes in a sterile container and the viable count determined. The viable counts in the biofilm were determined by placing the filter with the biofilm in 5 ml broth and disintegrating it with a vortex mixer. For *G. vaginalis* biofilms, the pH changed from 7.4 to 6.6 in BHI and MRS medium after overnight incubation. For *L. acidophilus* biofilms, the pH changed after overnight incubation from 7.4 to 6.9 in BHI medium and from 6.2 to 5.0 in MRS medium.

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The biofilm eradicating concentration (BEC) and the biofilm effluent minimum bactericidal concentrations (Ef MBC) defined as the concentrations that eliminated the organism from the biofilm and effluent, respectively, were calculated. The clindamycin BEC against *L. acidophilus* in MRS medium were 64 fold higher than in BHI medium (Table 1). This effect may be due to the change in pH of the MRS medium after overnight growth of *L. acidophilus*. The clindamycin BEC against *L. acidophilus* (1 to 64 µg/ml) was 62 to 4000 fold higher than against *G. vaginalis* (0.016 µg/ml). The effluent MBC for *L. acidophilus* (0.5 to 64 µg/ml) was also 125 to 16,000 fold higher than against *G. vaginalis* (0.004 µg/ml). Amoxicillin and erythromycin were active against *G. vaginalis* and *L. acidophilus* in biofilms. The metronidazole BEC and effluent MBC against *G. vaginalis* were the same (128 µg/ml). The activity of metronidazole against *L. acidophilus* was not measured. In summary, clindamycin was active against *Lactobacillus* biofilms *in vitro*. However, a 62 to 4000 fold higher concentration of drug was required to inhibit *Lactobacillus* than *G. vaginalis*.

Table 1: Tube MIC/MBC, BEC for biofilm, and effluent MBCs for *G. vaginalis* and *L. acidophilus* grown in BHI broth or MRS broth^a.

| Antibiotic, organism (broth type) | Tube MIC (mg/liter)/MBC (mg/liter) | Tube MBC/MIC ratio | BEC (mg/liter) | BEC: tube MBC ratio | Ef MBC (mg/liter) | Etest MIC (mg/liter) |
|---|------------------------------------|--------------------|----------------|---------------------|-------------------|----------------------|
| Amoxicillin | | | | | | |
| <i>G. vaginalis</i> | 0.06/0.06 | 1 | 32 | 512 | 4 | 0.016 |
| <i>L. acidophilus</i> (BHI) | ND/0.06 | ND | 1 | 16 | 1 | 0.19 |
| <i>L. acidophilus</i> (MRS) | 0.06/0.5 | 8 | 16 | 32 | 16 | 0.19 |
| Clindamycin | | | | | | |
| <i>G. vaginalis</i> | 0.004/0.008 | 2 | 0.016 | 2 | 0.004 | 0.016 |
| <i>L. acidophilus</i> (BHI) | ND/0.06 | ND | 1 | 16 | 0.5 | 0.016 |
| <i>L. acidophilus</i> (MRS) | 0.06/4 | 64 | 64 | 16 | 64 | 0.016 |
| Erythromycin | | | | | | |
| <i>G. vaginalis</i> | 0.004/0.03 | 8 | 1 | 32 | 0.5 | 0.016 |
| <i>L. acidophilus</i> (BHI) | ND/0.125 | ND | 4 | 32 | 2 | 0.032 |
| <i>L. acidophilus</i> (MRS) | 0.25/8 | 32 | >128 | >16 | >128 | 0.032 |
| Metronidazole (CO ₂), <i>G. vaginalis</i> | 8/32 | 4 | 128 | 4 | 128 | 8 |
| Metronidazole (An), <i>G. vaginalis</i> | 2/8 | 4 | ND | ND | ND | 2.0 |

^a Etests were done with DST agar plates as described in the text. Tests with *G. vaginalis* and metronidazole were done either in an atmosphere of 6% CO₂ or under anaerobic (An) conditions, as indicated. ND, not done; Ef MBC, effluent MBC.

For the tube broth dilution method, the same medium as in the biofilm experiment above was used. Medium containing different concentrations of drug were inoculated with 10⁵ cfu/ml of the bacteria and incubated overnight at 37°C under anaerobic conditions. The minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) were determined. The MIC was defined as the concentration that completely inhibited growth compared to drug free controls and MBC was defined as the concentration that inhibited growth upon subculture to drug free medium for 24 hours. The clindamycin MIC and MBC values against *G. vaginalis* were 0.004 and 0.008 µg/ml, respectively (Table 1). The clindamycin MIC and MBC values against *L. acidophilus* were 15-fold, and 7.5 to 500 fold higher than against *G. vaginalis*, respectively. Amoxicillin and erythromycin were active against *G. vaginalis* and *L. acidophilus* with an MIC of 0.06 and <0.25 µg/ml, respectively. Against *G. vaginalis*, the metronidazole MIC was <8 µg/ml. The activity of metronidazole against *L. acidophilus* was not measured.

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The activity of clindamycin against *G. vaginalis* and *L. acidophilus* in biofilms (expressed as BEC) was compared to that observed using the broth dilution method (expressed as MBC). The clindamycin BEC value against *G. vaginalis* was 2 fold higher than the MBC value. In the case of *L. acidophilus*, the BEC value was 16 fold higher than the MBC value, suggesting a higher concentration of the drug is required to kill *L. acidophilus* and *G. vaginalis* in biofilms.

E-test was performed using test kits manufactured by Biodisk (Sweden). Testing was performed according to manufacturer's instruction, however, the Diagnostic sensitivity test (DST) agar was used instead of the medium (Wilkins Chalgren or Brucella agar supplemented with 5% defibrinated sheep blood and vitamin K1) proposed by the manufacturer. *B. fragilis* strain NCTC 9343 was used as a control strain for E-test. The MIC for *B. fragilis* was stated to be 0.5 µg/ml, however, it is unclear if this MIC value is for all antibacterial agents or for one of the 4 antibacterial agents tested. The clindamycin MIC against *G. vaginalis* and *L. acidophilus* by the E-test method was 0.016 µg/ml, suggesting that the drug is active against both *G. vaginalis* and *L. acidophilus* (Table 1). Against *G. vaginalis*, the metronidazole MIC was 8 µg/ml and similar to that observed in the tube broth dilution method. The activity of metronidazole against *L. acidophilus* was not measured.

In another study (Aroutcheva *et al.*, 2001, Infect Dis Obstet Gynecol, 9: 239-244), the activity of clindamycin against 4 clinical isolates of *Lactobacillus* species (1 *L. acidophilus*, 2 *L. casei casei*, 2 *L. casei rhamnosus*, 1 *L. jensenii*) was examined by the broth dilution method. The MRS broth medium was used for susceptibility testing. Cultures (10^5 cfu/ml) were incubated in the presence of clindamycin at 37°C and the optical density (OD) measured spectrophotometrically every 4 hours up to 48 hours. The MIC defined as the concentration of the drug required to completely inhibit growth was determined. The growth of *L. acidophilus* at different concentrations of clindamycin is shown in Table 2 and Figure 1. At clindamycin concentration of 1000-3000 µg/ml, the growth of *L. acidophilus* is completely inhibited over a 48 hour incubation period. These MIC values are high compared to the previous study using the same media (MIC = 0.06 µg/ml). The authors have stated that this concentration of clindamycin is 100 times lower than that obtained during intravaginal administration of clindamycin (2% cream) for 7 days and may further suppress growth of *Lactobacillus* species in BV patients. No other antibacterial drug approved for BV was used as a comparator.

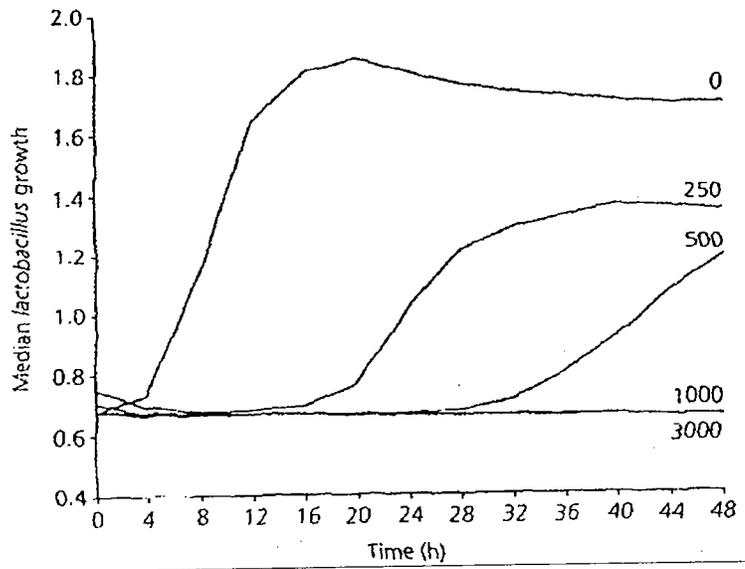
Table 2: Growth of *Lactobacillus* (mean optical density values ± standard deviation) with different clindamycin concentrations.

| Time (h) | Clindamycin concentration | | | | | | | |
|----------|---------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | 0 | 31.25 µg/ml | 62.5 µg/ml | 125 µg/ml | 250 µg/ml | 500 µg/ml | 1000 µg/ml | 3000 µg/ml |
| 12* | 1.68 ± 0.4 1.83 | 1.27 ± 0.33 1.34 | 0.91 ± 0.28 0.83 | 0.69 ± 0.01 0.68 | 0.68 ± 0.02 0.68 | 0.67 ± 0.01 0.68 | 0.67 ± 0.01 0.67 | 0.67 ± 0.01 0.67 |
| 24 | 1.82 ± 0.53 1.95 | 1.68 ± 0.49 1.87 | 1.36 ± 0.52 1.52 | 0.89 ± 0.33 0.68 | 1.01 ± 0.29 1.08 | 0.67 ± 0.01 0.67 | 0.66 ± 0.01 0.66 | 0.66 ± 0.01 0.67 |
| 36 | 1.72 ± 0.49 1.80 | 1.62 ± 0.47 1.72 | 1.50 ± 0.42 1.68 | 1.21 ± 0.44 1.35 | 1.33 ± 0.52 1.59 | 0.79 ± 0.21 0.70 | 0.66 ± 0.01 0.66 | 0.66 ± 0.01 0.66 |
| 48 | 1.70 ± 0.46 1.79 | 1.59 ± 0.46 1.67 | 1.50 ± 0.44 1.62 | 1.30 ± 0.35 1.47 | 1.34 ± 0.51 1.62 | 1.18 ± 0.47 1.26 | 0.66 ± 0.01 0.66 | 0.66 ± 0.01 0.66 |

Mean value of initial OD for 0 time was 0.7

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Figure 1: Median *Lactobacillus* growth in varying concentrations ($\mu\text{g/ml}$) of clindamycin.

3.3. Activity *in vivo*:

No studies were conducted to evaluate the activity of clindamycin against the organisms associated with BV *in vivo*.

3.4. Drug Resistance and Cross-resistance:

In vitro, plasmid-mediated transfer of clindamycin resistance phenotype has been reported in *B. fragilis* (Shimell *et al.*, 1982, J. Bacteriol. 152: 950-953; Smith and Macrina *et al.*, 1984, J. Bacteriol. 158: 739-741). However, the clinical relevance of this finding is unknown.

4. CLINICAL MICROBIOLOGY:

4.1. Study 02-005:

This was a multicenter, randomized, double-blind, parallel group study conducted to evaluate the safety and efficacy of _____ in 262 non-pregnant women (≥ 18 years of age) with bacterial vaginosis. Subjects exhibiting signs and symptoms of bacterial vaginosis i.e., characteristic homogenous off-white discharge without inflammation, vaginal pH > 4.5 , $\geq 20\%$ clue cells in wet mount slides, and positive KOH whiff test were enrolled. Subjects with a gram stain nugent score < 4 [which is based on the morphotype score of the type of organisms (*Lactobacilli*, *Gardnerella/Bacteroides*, and *Mobiluncus* species) observed under oil immersion field in a smear made using a vaginal swab] were excluded. Subjects with cervical neoplasia or vulvovaginal or genital infections such as bacterial vaginosis, trichomonal vaginitis, gonorrhoea, chlamydia or genital herpes were also excluded. Patients were randomized (1:1:1) to receive a single dose of _____ (100 mg) or metronidazole cream 0.75% (37.5 mg, manufactured by _____) or placebo, intravaginally.

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The primary efficacy endpoint was therapeutic cure (clinical cure and a gram stain nugent score ≤ 3) at 21-30 days after discontinuation of therapy. Clinical cure was defined as the resolution of clinical signs and symptoms with normal vaginal discharge (negative whiff test, negative for clue cells in wet mount, and a normal vaginal pH of < 4.7). The secondary efficacy endpoints were (a) analysis of clinical cure rates, and (b) analysis of patients with a gram stain nugent score of < 4 , separately.

The subjects were evaluated for clinical and microbiologic outcomes using vaginal specimens at baseline and at the test of cure visit (21-30 days after discontinuation of therapy). Microbiologic measurements using vaginal specimens included (1) wet mount and gram stain examination, (2) 10% KOH whiff test, and (3) vaginal pH determination. The gram stain was performed at the

Of the 262 patients that were randomized, 255 received the drug (intent-to-treat population, ITT). Of these 255, 216 had a nugent score of ≥ 4 at baseline (modified intent to treat population, mITT). Patients were considered evaluable if they met the inclusion exclusion criteria and did not use any other intravaginal product for the first 7 days after dosing. Therapeutic cure was observed in 38% patients treated with _____ compared to 23% with metronidazole and 0% with placebo, at 21-30 days after discontinuation of therapy (Table 3). The clinical cure rates (47% _____ arm, 35% metronidazole arm, and 21% placebo arm) and the cure by nugent criteria (55% _____ arm, 29% metronidazole arm, and 2% placebo arm) were higher than that based on combined clinical cure and nugent criteria. The activity of clindamycin against the different bacterial species associated with BV could not be analyzed as the bacteria at baseline and post-treatment were not speciated and only nugent scores were determined.

Table 3: Efficacy of _____ to Metronidazole and placebo in evaluable BV population in study 02-005.

| Outcome | _____ | Metronidazole | Placebo |
|-------------------------|-------------|---------------|------------|
| Therapeutic cure | 20/53 (38%) | 11/48 (23%) | 0/42 (0%) |
| Clinical cure | 25/53 (47%) | 17/48 (35%) | 9/42 (21%) |
| Cure by Nugent criteria | 29/53 (55%) | 14/48 (29%) | 1/42 (2%) |

4.2. Study 01-025:

In another multicenter, randomized, single-blind, parallel group study (Protocol #01-025), the safety and efficacy of a single dose of 2% Clindamycin site release[®] vaginal cream was compared to Cleocin[®] cream (administered once a day for 7 days) in 350 patients with bacterial vaginosis. The inclusion and exclusion criteria, endpoints, and methods used for clinical and microbiological evaluations were same as in study 02-005.

Therapeutic cure was observed in 41% patients treated with _____ compared to 46% with Cleocin, at 21-30 days after initiation of therapy (Table 4). The clinical cure rates and cure rates based on nugent score were similar in the two groups but higher than the therapeutic cure rates. Only nugent scores were obtained and speciation of bacteria at baseline and post-treatment was not done. Hence, the activity of clindamycin against the different bacterial species associated with BV could not be analyzed.

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Table 4: Efficacy of [REDACTED] and Cleocin in evaluable BV population in study 01-025.

| Outcome | [REDACTED] | Cleocin* |
|-------------------------|--------------|--------------|
| Therapeutic cure | 53/128 (41%) | 57/125 (46%) |
| Clinical cure | 81/128 (63%) | 79/125 (63%) |
| Cure by Nugent criteria | 70/128 (55%) | 71/125 (57%) |

outcomes measured at 21 - 30 days after discontinuation of [REDACTED] single dose) therapy

* outcomes measured at 14 - 21 days after discontinuation of Cleocin (7 day) therapy

Overall, the two studies show that the efficacy of [REDACTED] is similar to Cleocin and superior to placebo in the treatment of bacterial vaginosis. The activity of clindamycin against the different bacteria species associated with BV could not be analyzed as the bacteria at baseline and post-treatment were not speciated and only nugent scores were determined. However, the cure by nugent score suggests that there was an increase in *Lactobacillus* morphotypes and decrease in the *Gardnerella*, *Bacteroides* and *Mobiluncus* morphotypes in 55% patients at 21-30 days after discontinuation of treatment with [REDACTED].

4.3. Effect of clindamycin on vaginal colonization by *Lactobacillus*:

The effect of clindamycin on vaginal colonization by *Lactobacillus* was examined in patients with BV (Agnew and Hillier, 1995, Sex. Trans Dis, 22: 269-273). Patients were treated with 2% clindamycin vaginal cream (once daily for 7 days) or 0.75% metronidazole vaginal gel (twice daily for 5 days). The vaginal swabs from patients at baseline, 1 week (end of therapy), and ≥ 1 month after initiation of therapy were examined by gram stain and culture. The lactobacilli were identified by gram stain and colony morphology in Columbia 5% sheep blood agar medium or Rogosa agar. Cultures in Columbia 5% sheep blood agar medium were incubated in 5-7% CO₂ at 37°C for 48-72 hours. Cultures in Rogosa agar were incubated at 37°C in an anaerobic chamber for 5 days. No attempts were made to identify the species of *Lactobacillus* or quantify the lactobacilli. However, the ability of the isolate to produce hydrogen peroxide (H₂O₂) was determined using a tetra-methylbenzidine agar medium.

The number of patients with lactobacilli at baseline, end of therapy (EOT), and ≥ 1 month after initiation of therapy are shown in Table 5. The number of patients with H₂O₂ producing lactobacilli or non H₂O₂ producing lactobacilli in Table 5 included patients with mixed lactobacilli (H₂O₂ producers and non-producers). It would have been useful to analyze the number of patients with mixed lactobacilli (i.e., both H₂O₂ producers and non-producers) separately. A decrease was observed in the number of patients with lactobacilli at EOT with clindamycin compared to baseline (Table 5). However, the number of patients with lactobacilli at ≥ 1 month after initiation of therapy increased. In the case of metronidazole treated patients, an increase was observed in the number of patients with lactobacilli at EOT and ≥ 1 month after initiation of therapy compared to baseline. The colonization of lactobacilli at ≥ 1 month after initiation of therapy was observed in 87% and 94% patients treated with clindamycin and metronidazole, respectively. The results suggest that clindamycin caused a transient decrease in lactobacilli at EOT followed by an increase in lactobacilli colonization at ≥ 1 month after initiation of therapy.

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Table 5: Effect of treatment for vaginitis and cervicitis on vaginal colonization by lactobacilli (LB).

| Treatment | Number of patients (n) | LB | Baseline (% patients with lactobacilli) | EOT (% patients with lactobacilli) | ≥ 1 month after initial therapy (% patients with lactobacilli) |
|-----------------------|------------------------|-----------------------------------|--|---------------------------------------|---|
| Clindamycin vaginal | 28 | All | 50 | 25 | 87 |
| | | H ₂ O ₂ +ve | 29 | 11 | 57 |
| | | H ₂ O ₂ -ve | 25 | 21 | 17 |
| Metronidazole vaginal | 18 | All | 67 | 83 | 94 |
| | | H ₂ O ₂ +ve | 22 | 61 | 59 |
| | | H ₂ O ₂ -ve | 56 | 67 | 71 |

LB = *Lactobacillus*;

EOT = end of therapy;

All = H₂O₂ +ve and -ve lactobacilliH₂O₂ +ve = patients having hydrogen peroxide producing lactobacilli exclusively or in addition to lactobacilli which do not produce hydrogen peroxide;H₂O₂ -ve = patients that have lactobacilli which do not produce hydrogen peroxide exclusively or in addition to lactobacilli that produce hydrogen peroxide.

In another study (Hillier *et al.*, 1990, *Obstet Gynecol.* 76: 407-413), the bacteria associated with bacterial vaginosis in vaginal wash specimens of clindamycin or placebo treated BV patients was quantified. Patients were treated with 2% clindamycin vaginal cream or placebo, administered once daily for 7 days. A vaginal wash specimen was obtained by instilling balanced salt solution into the vagina, mixing using a sterile swab, and collecting the specimen with a syringe, at baseline, EOT, and 1 month after initiation of therapy. The vaginal wash suspension was diluted and plated on Brucella agar supplemented with 5% sheep blood, vitamin K, and hemin, or heart infusion agar supplemented with 5% sheep blood. The cultures were incubated at 37°C in a 5-7% CO₂ atmosphere for 48 hours and the colony forming units (CFU) per ml of vaginal fluid was determined.

The lactobacilli cfu/ml at baseline in patients treated with placebo were higher than that of patients treated with clindamycin. At EOT and follow-up (1 month after initiation of therapy), the median cfu/ml for *Lactobacilli* increased compared to baseline. However, the median cfu/ml for *G. vaginalis*, *Bacteroides* sp and *Peptostreptococcus* sp decreased at EOT and follow-up compared to baseline (Table 6). In placebo treated patients, the cfu/ml of all the 4 bacterial species did not change significantly from baseline at EOT. The placebo patients were not followed beyond EOT.

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Table 6: Median concentration of microorganisms among bacterial vaginosis patients with positive isolates at baseline, end of therapy (EOT) and 1 month after initiation of treatment with clindamycin or placebo.

| Bacteria and treatment | Baseline (cfu/ml) | EOT (cfu/ml) | 1 month after initiation of therapy (cfu/ml) |
|------------------------------|-------------------|-------------------|--|
| <i>G. vaginalis</i> | | | |
| 2% clindamycin | 10 ^{9.3} | 10 ^{4.3} | 10 ^{6.2} |
| placebo | 10 ^{9.3} | 10 ^{9.5} | ND |
| <i>Lactobacillus</i> | | | |
| 2% clindamycin | 10 ^{4.5} | 10 ^{7.3} | 10 ^{7.5} |
| placebo | 10 ^{7.3} | 10 ^{7.0} | ND |
| <i>Bacteroides</i> sp | | | |
| 2% clindamycin | 10 ^{7.9} | 10 ^{5.1} | 10 ^{3.7} |
| placebo | 10 ^{7.0} | 10 ^{8.5} | ND |
| <i>Peptostreptococcus</i> sp | | | |
| 2% clindamycin | 10 ^{7.4} | 10 ^{6.2} | 10 ^{3.3} |
| placebo | 10 ^{6.4} | 10 ^{6.5} | ND |

Cfu/ml = colony forming units per milliliter.

In summary, the clindamycin MBC against *L. acidophilus* was 32 fold higher than against *G. vaginalis* in broth. Using biofilms, the activity of clindamycin against *L. acidophilus* was 62 to 4000 fold lower than *G. vaginalis*. Clindamycin does exhibit some activity against *Lactobacillus in vitro*. One study does show that clindamycin may have a transient inhibitory effect on lactobacilli colonization. Such an inhibitory effect appears to be reversed leading to increased colonization with lactobacilli, 3 weeks after discontinuation of therapy. The second study did not show such a transient inhibition of vaginal lactobacilli.

5. CONCLUSIONS:

The sponsor is seeking approval of [REDACTED][™] for the treatment of bacterial vaginosis based on published literature, the approved label for Cleocin[®] vaginal cream, and 2 well-controlled clinical studies in patients with BV.

[REDACTED] and Cleocin[®], both contain 2% clindamycin phosphate that is hydrolyzed *in vivo* to the active ingredient, clindamycin. *In vitro*, clindamycin is active against most strains of *Gardnerella vaginalis*, *Mycoplasma hominis*, *Bacteroides* sp, *Mobiluncus* sp, and *Peptostreptococcus* sp., which are associated with BV.

The clindamycin MBC against *L. acidophilus* was 32 fold higher than against *G. vaginalis* in broth. In the vagina, bacteria adhere to the epithelial cells and may be considered as forming a biofilm. Using biofilms established *in vitro*, the activity of clindamycin against *L. acidophilus* was 62 to 4000 fold lower than *G. vaginalis*. Clindamycin does exhibit some activity against *Lactobacillus in vitro*. Of the 2 studies that evaluated the effect of clindamycin on vaginal lactobacilli colonization, one study showed a transient decrease in colonization at end of therapy while the other did not. Such an effect appeared to be reversed with increased lactobacilli colonization at 3 weeks after discontinuation of therapy.

In clinical studies, the efficacy of [REDACTED] was similar to Cleocin and superior to placebo in the treatment of bacterial vaginosis. The studies only provided information on the nugent scores

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KV Pharmaceutical Company

using vaginal swabs at baseline and post-treatment. No information was available on the species of bacteria at baseline and post-treatment in patients enrolled in the clinical studies. Therefore, the activity of clindamycin against the bacterial species associated with BV could not be analyzed in the clinical studies. The cure by nugen score suggests that there was an increase in *Lactobacillus* morphotypes and decrease in the *Gardnerella*, *Bacteroides* and *Mobiluncus* morphotypes in 55% patients at 21-30 days after treatment with [REDACTED].

6. LABEL:

6.1. Sponsor's proposed label:

MICROBIOLOGY

Clindamycin inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the process of peptide chain initiation. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis (See INDICATIONS AND USAGE). Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis*, *Mobiluncus* spp., or *Mycoplasma hominis*, has not been defined. Nonetheless, clindamycin is an antimicrobial agent active *in vitro* against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

Bacteroides spp.

Gardnerella vaginalis

Mobiluncus spp.

Mycoplasma hominis

Peptostreptococcus spp.

INDICATIONS AND USAGE

[REDACTED] is indicated for the single-day, single-dose, treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis) in non-pregnant women. There are no adequate and well-controlled studies of [REDACTED] in pregnant women.

NOTE:

For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater than 4.5, (b) emits a "fishy" amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram's stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent *Lactobacillus* morphology, (b) predominance of *Gardnerella* morphotype, and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, eg, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *N. gonorrhoeae*, *Candida albicans*, and *Herpes simplex* virus should be ruled out.

6.2. Comments:

[REDACTED]

Clindamycin

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7. RECOMMENDATIONS:

The NDA submission should be approved with respect to Microbiology for the treatment of bacterial vaginosis. There are no changes to the Microbiology section of the label.

Kalavati Suvarna
Microbiologist, HFD-590

CONCURRENCES:

HFD-590/Deputy Dir _____ Signature _____ Date _____
HFD-590/Micro TL _____ Signature _____ Date _____

CC:

HFD-590/Original IND

HFD-590/Division File

HFD-590/MO

HFD-590/Pharm

HFD-590/Chem

HFD-590/Review Micro

HFD-590/CSO/PeacockS

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/s/

Kalavati Suvarna
7/30/04 01:01:20 PM
MICROBIOLOGIST

Shukal Bala
7/30/04 01:04:04 PM
MICROBIOLOGIST

Steve Hundley
8/1/04 12:45:24 PM
PHARMACOLOGIST

Product Quality Microbiology Review

Review for HFD-590

26 MAY 2004

NDA: 50-793

Drug Product Name

Proprietary: _____

Non-proprietary: clindamycin phosphate vaginal cream, 2.0%

Drug Product Priority Classification: S

Review Number: 1

Subject of this Review

Submission Date: 30 October 2003

Receipt Date: 31 October 2003

Consult Date: 30 March 2004

Date Assigned for Review: 28 April 2004

Submission History (for amendments only)

Date(s) of Previous Submission(s): N/A

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: KV Pharmaceuticals

Address: 2503 South Hanley Rd, St Louis, MO 63144

Representative: Herbert Luther, Ph.D.

Telephone:

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUPPLEMENT:** N/A
 2. **SUPPLEMENT PROVIDES FOR:** N/A
 3. **MANUFACTURING SITE:** N/A
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Non-Sterile vaginal cream, 2.0% clindamycin phosphate
 5. **METHOD(S) OF STERILIZATION:** N/A
 6. **PHARMACOLOGICAL CATEGORY:** Antimicrobial
- B. **SUPPORTING/RELATED DOCUMENTS:** NDA 50-793/BC amendment dated 6 April 2004 (contained results of anti-microbial effectiveness test).
- C. **REMARKS:** This submission was a 505(b)(2) application submitted in the CTD format.

filename: 50793.doc

Executive Summary

I. Recommendations

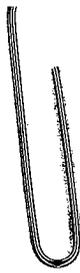
- A. Recommendation on Approvability** – This submission is recommended for approval on the basis of product quality microbiology.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is a non-sterile, preserved, topical cream. The drug product has microbial limit release specifications.
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Microbiology Supervisor
- C. CC Block**
N/A



 1 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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/s/

Bryan Riley
6/21/04 02:35:27 PM
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