DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Scarlett Tumulty
Associate Director, Regulatory Affairs
KV Pharmaceutical Company
2503 South Hanley Road
St. Louis, MO 63144

RE: NDA # 50-793
Clindesse™ (clindamycin phosphate) Vaginal Cream, 2%
MACMIS ID # 15021

Dear Ms. Tumulty:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed an e-Pharm/alert e-mail for Clindesse (clindamycin phosphate) Vaginal Cream, 2% announcing "Clindesse at UnitedHealthcare® On formulary" submitted by KV Pharmaceutical Company (KV) under cover of Form FDA 2253. The e-Pharm/alert e-mail is false or misleading because it overstates and misrepresents the efficacy of Clindesse, presents unsubstantiated superiority and patient compliance claims, and minimizes the risks and limitations to the indication associated with Clindesse. Thus, the e-Pharm/alert e-mail misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & (n). *Cf.* 21 CFR 202.1(e)(5)(ii); (e)(6)(i), (ii), (vii), (x); (e)(7)(i), (iv), (viii). These violations are concerning from a public health perspective because they suggest that Clindesse is more effective than has been demonstrated.

Background

According to the approved product labeling (PI):

> Clindesse is indicated for the 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 Clindesse 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, e.g., *Trichomonas vaginalis*, *Chlamydia trachomatis*, *N. gonorrhoeae*, *Candida albicans*, and *Herpes simplex* virus should be ruled out.

The Microbiology section of the PI states (in pertinent part):

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. 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.

The Clinical Studies section of the PI states:

Two clinical studies were conducted to evaluate the efficacy of Clindesse for the treatment of bacterial vaginosis. In one clinical study involving 144 patients with a baseline Nugent score ≥ 4, Clindesse demonstrated superior efficacy over placebo intravaginal cream as measured by therapeutic cure, clinical cure, and Nugent score cure (Table 2). Therapeutic cure was a composite endpoint which required both clinical cure and Nugent score cure. Clinical cure required normal vaginal discharge, vaginal pH < 4.7, < 20% clue cells on wet mount preparation, and negative "whiff" test (detection of amine odor on addition of 10% KOH to sample of the vaginal discharge). A Nugent score of 0-3 was considered a Nugent score cure. The Nugent scoring is based on microscopic examination of the Gram's stained vaginal smears for quantification of specific bacterial morphotypes.

Table 2. Efficacy of Clindesse™ for Treatment of Bacterial Vaginosis in a Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study

	Clindesse™	**Placebo**	**Treatment**
Outcome	**N=78**	**N=66**	**Difference† (%) [97.5%**
	% Cure	**% Cure**	**Confidence Interval]**
Therapeutic Cure‡	29.5	3.0	26.5 [14.0, 39.0]
Clinical Cure	41.0	19.7	21.3 [4.7, 38.0]
Nugent Score Cure	44.9	6.1	38.8 [24.6, 53.1]

N=number of patients in treatment group (modified intent-to-treat population defined as all subjects randomized who received at least one dose of study medication, and who had a baseline Nugent score of at least 4)

†Treatment difference=Clindesse™ minus placebo cure rates

‡Primary efficacy outcome measure

In a second controlled clinical study involving 432 patients with a baseline Nugent score of ≥4, 221 women self-administered a single dose of Clindesse, and 211 women self-administered a single daily dose of Cleocin Vaginal Cream 2% for 7 days. A single dose of Clindesse was shown to be similar to 7 daily doses of Cleocin Vaginal Cream 2% for treatment of bacterial

vaginosis as measured by therapeutic cure, clinical cure or Nugent score cure (Table 3). The study endpoints were identical to those described above for the placebo-controlled study.

The cure rates reported in the clinical studies with Clindesse were based on resolution of 4 out of 4 Amsel criteria and a Nugent score of < 4, while the criteria for cure in previous clinical studies with Cleocin Vaginal Cream were based solely on resolution of 2 out of 4 Amsel criteria, resulting in higher reported rates of cure for bacterial vaginosis.

Table 3. Efficacy of Clindesse™ in Treatment of Bacterial Vaginosis in a Randomized, Investigator-Blind, Active-Controlled Comparative Study

Outcome	Clindesse™ Single dose N=221 % Cure	Cleocin® Vaginal Cream (7 doses) N=211 % Cure	Treatment Difference† (%) [95% Confidence Interval]
Therapeutic Cure‡	33.0	37.0	–3.9 [–12.9, 5.1]
Clinical Cure	53.4	54.0	–0.6 [–10.0, 8.8]
Nugent Score Cure	45.7	49.3	–3.6 [–13.1, 5.8]

†Treatment difference=Clindesse™ minus Cleocin® Vaginal Cream cure rates N=number of patients in treatment group (modified intent-to-treat population defined as all subjects randomized who received at least one dose of study medication, and who had a baseline Nugent score of at least 4) ‡Primary efficacy outcome measure

Table 4. Efficacy of Clindesse™ in Treatment of Bacterial Vaginosis in a Randomized, Investigator-Blind, Active-Controlled Comparative Study—Per Protocol

Outcome	Clindesse™ Single dose N=221 % Cure	Cleocin® Vaginal Cream (7 doses) N=211 % Cure	Treatment Difference† (%) [95% Confidence Interval]
Therapeutic Cure‡	42.1	45.6	-3.5 [-15.8, 8.7]
Clinical Cure	64.3	63.2	1.1 [-10.8, 13.0]
Nugent Score Cure	56.5	57.7	-1.3 [-13.6, 11.1]

†Treatment difference=Clindesse™ minus Cleocin® Vaginal Cream cure rates
N=number of patients in treatment group (per protocol population defined as all
subjects included in the modified intent-to-treat population who completed the
study without significant protocol violation)
‡Primary efficacy outcome measure
§Four subjects (2 from each treatment group) did not have complete Nugent
scores and were not included in the Nugent Score cure analysis

Overstatement of Efficacy/Misleading Efficacy Presentation

The e-Pharm/alert e-mail is misleading because it claims that Clindesse is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The piece includes the claims:

- "Clindesse delivers 88% efficacy and one-dose convenience[1,2]" (page 1; references 1 and 2 below)
- "88% clinical cure rate[1]" (page 1; reference 1 below)
- "Just one & dosing's done…Clindesse delivers 88% efficacy and one dose convenience[1,2]" (page 2; references 1 and 2 below)
- Bar graph titled "Clinical cure rate for BV[1]" showing 88% of patients with "3 of 4 Amsel criteria resolved."
    - Text below the bar graph states: "Current CDC guidelines recommend evaluating BV based on resolution of 3 of 4 Amsel criteria.[5] Multicenter, randomized, parallel-group study of patients with BV. 128 Clindesse patients were evaluated from the per-protocol population.[1]" (Page 2; references 1 and 4 below)

These claims overstate the efficacy of Clindesse because they are inconsistent with the efficacy information provided in the Clindesse PI and misrepresent the definition of clinical cure for bacterial vaginosis (BV). The studies cited in the Clinical Studies section of the PI defined clinical cure as resolution of 4 out of 4 of the Amsel criteria: "normal vaginal discharge, vaginal pH < 4.7, < 20% clue cells on wet mount preparation, and negative "whiff" test (detection of amine odor on addition of 10% KOH to sample of the vaginal discharge)." Consequently, clinical cure rates in these clinical studies for Clindesse ranged from 41% to 64.3%[3] based on this definition, not 88% as claimed in the e-Pharm/alert email. Although the publication of Study 01-025 by Faro S, et al. reported that 88% of patients treated with Clindesse had 3 of 4 Amsel criteria resolved and that this finding was consistent with the comparator arm, both of the studies supporting approval of Clindesse (Study 01-025 and Study 02-005), as well as Faro S, et al., defined "clinical cure" as resolution of 4 out of 4 Amsel criteria. The 2002 Sexually Transmitted Disease (STD) CDC treatment guidelines[4] referenced do not "recommend evaluating BV based on resolution of 3 of 4 Amsel criteria" (emphasis added). These guidelines, as well as the more recent 2006 STD CDC treatment guidelines[5], recommend diagnosis based on the presence of 3 out of 4 clinical (Amsel) criteria. Neither set of guidelines provides recommendations for the evaluation of BV cure based on resolution of Amsel criteria.

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[1] Faro S, Skokos CK. The efficacy and safety of a single dose of Clindesse vaginal cream versus a seven-dose regimen of Cleocin vaginal cream in patients with bacterial vaginosis. *Infect Dis Obstet Gynecol.* 2005; 13:155-160.

[2] Clindesse (clindamycin phosphate) Vaginal Cream, 2% prescribing information.

[3] Clinical cure rates as reported in the Clinical Studies section of the Clindesse PI. Adapted from Table 2 (Clindesse vs Placebo; ,modified intent-to-treat population), Table 3 (Clindesse vs Cleocin; modified intent-to-treat population), and Table 4 (Clindesse vs Cleocin; per protocol population).

[4] Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines. MMWR Morb Mortal Wkly Rep. 2002;51:42-44.

[5] Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines. MMWR Morb Mortal Wkly Rep. 2006;55:50-52.

In addition, the claim, "Clindesse effectively relieves the vaginal odor associated with BV in just 1.5 days[3]" (reference 6 below) is not supported by substantial evidence or substantial clinical experience. The data on file[6] references Study 01-025 and is based on patient self-reported information (patient diaries) recorded daily during the study. Time to vaginal odor relief as perceived by the patient was not a prespecified outcome measure in the study. The prespecified outcome measures of this study were based on investigator/physician assessment 21-30 days post initial dose of study medication of both Amsel criteria and Nugent score. Because BV may be asymptomatic in more than half of affected patients and because symptom presentation is variable in patients with symptoms,[5] subjective symptom resolution was not used as an outcome measure in Study 01-025. Instead, more objective and comprehensive measures such as Amsel criteria and Nugent score were deemed necessary. Study 01-025 prespecified clinical markers such as the Amsel clinical criteria and surrogate markers such as the Nugent score as study endpoints. Reduction of vaginal odor alone was not a recognized endpoint.

Unsubstantiated Superiority Claims/ Unsubstantiated Claims

The e-Pharm/alert e-mail is misleading because it claims that Clindesse is superior to metronidazole when this has not been demonstrated by substantial evidence or substantial clinical experience. Page 3 of the e-Pharm/alert e-mail presents the following claim:

- "Clindamycin has demonstrated better activity than metronidazole against 3 of the most common pathogens implicated in BV[7, 8, 9, 10]" (references 7, 8, 9, and 10 below)
  - *Gardnerella vaginalis*
  - *Mobiluncus* spp
  - *Mycoplasma hominis*

This claim is misleading because it suggests that Clindesse, as a formulation of clindamycin, is more effective than any metronidazole formulation because of clindamycin's purported superior activity against the most common pathogens in BV. The references cited[7, 8, 9, 10] do not provide substantial evidence to support any claims of superior *in vitro* activity or superior clinical effectiveness of clindamycin or Clindesse over metronidazole. None of the references cited presents data evaluating the Clindesse formulation of clindamycin, nor do the data discussed in these references include a head-to-head comparison of any clindamycin formulation to any metronidazole formulation. Briefly, Wilson et al.,[7] is a review of the etiology and management of recurrent BV. The publication provides no evidence to support this superiority claim. Ugwumadu et al.,[8] examined the effect of an oral

[6] Data on file. Ther-Rx Corporation.

[7] Wilson J. Managing recurrent bacterial vaginosis, *Sex Transm Infect.* 2004;80:8-11.

[8] Ugwumadu A, Manyonda I, Reid F, Hay P. Effects of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomized controlled trial. *Lancet.* 2003;261:983-988.

[9] Hillier S, Krohn MA, Watts H, Wolner-Hanssen P., Eschenbach D. Microbiologic efficacy of intravaginal clindamycin cream for the treatment of bacterial vaginosis. *Obstet Gynecol.* 1990; 76:407-413.

[10] Smayevsky J, Canigia L, Lanza A, Bianchini H. Vaginal microflora associated with bacterial vaginosis in nonpregnant women: reliability of sialidase detection. I*nfect Dis Obstet Gynecol.* 2001;9:17-22.

clindamycin capsule versus placebo on pregnancy outcome (late miscarriage and spontaneous preterm delivery), not BV. Hillier et al.,[9] studied non-pregnant women with BV randomized to treatment with one of three different clindamycin (0.1, 1, or 2%) vaginal cream strengths or placebo cream for 7 days. Finally, Smayevsky, et al.,[10] did not evaluate BV treatment but reported the prevalence of various bacteria from women with and without BV. None of the references provides any *in vitro* or direct clinical comparison of clindamycin to metronidazole. Even if the references cited did present data to support the statement that Clindesse demonstrated better *in vitro* activity than metronidazole, such *in vitro* data would not constitute substantial evidence to support a claim or implication of superior clinical effectiveness. The statement, "*In vitro* activity does not necessarily imply clinical effectiveness" does not mitigate this misleading impression that clindamycin, or Clindesse in particular, is superior to metronidazole.

Furthermore, this claim is misleading because there is no standard methodology for determining antibiotic susceptibility to *Gardnerella vaginalis*, *Mobiluncus* spp., and *Mycoplasma hominis.* The Microbiology section of the Clindesse PI states:

> Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens *Gardnerella vaginalis*, *Mobiluncus* spp., or *Mycoplasma hominis*, has not been defined.

FDA is not aware of substantial evidence or substantial clinical experience to support the claim that Clindesse is superior to metronidazole. If you have data to support this claim, please submit the data to FDA for review.

The e-Pharm/alert email is misleading because it claims that Clindesse improves and enhances patient compliance[11] compared to other products indicated for the treatment of bacterial vaginosis and, as a result of superior compliance, is more effective than those products:

- "Improvement in compliance may be associated with improved effectiveness[4]" (page 3; reference 12 below)

The claim is misleading because Clindesse has not been shown to be more effective than any other products indicated for the treatment of bacterial vaginosis whether or not compliance was improved. First, the Merabet et al. publication[12] that is cited as support for the claim is a review article of the evolution of vaginal drug delivery technology and treatment options for bacterial vaginosis and vulvovaginal candidiasis. The article provides no clinical data to support claims that Clindesse offers superior effectiveness as compared to other treatment options. Merabet et al. discusses aspects of Study 01-025, but that study does not support a claim of superior effectiveness for Clindesse. Study 01-025 showed no statistically significant difference between Clindesse and its comparator (Cleocin) in any of the efficacy outcomes measured (see Tables 3 and 4 in the Clinical Studies section of the Clindesse PI). Furthermore, patients in Study 01-025 treated with Clindesse (one dose) did not experience "enhanced" or "improved" effectiveness compared to Cleocin (seven daily doses) in the

[11] "Single, anytime dosing and minimal leakage for enhanced patient compliance[3,4]" (page 1) (citing to reference 6, above, and reference 12, below)

[12] Merabet J, Thompson D, Levinson RS. Advancing vaginal drug delivery. Expert Opin. Drug Deliv. 2005;2:769-777.

modified intent-to-treat population, which consisted of patients who received at least one dose of study medication (i.e., this population represents completed Clindesse therapy but varying degrees of compliance with Cleocin therapy). According to the PI, the clinical cure rate in the modified intent-to-treat population for Clindesse was 53.4% vs 54% for Cleocin.

We are thus unaware of any data to support this claim of superior compliance and effectiveness. If you have any data to support it, please submit them to FDA for review.

This unsubstantiated superiority claim is exacerbated by the misleading presentation of efficacy data in the Pharm/alert e-mail. As discussed above, the Pharm/alert e-mail presents a series of claims about the clinical cure rate for Clindesse ("delivers 88% efficacy," "88% clinical cure rate," bar graph titled "Clinical cure rate for BV" showing 88% of Clindesse patients with "3 of 4 Amsel criteria resolved"[13]) based on Study 01-025, but fails to present the results for Cleocin. Failure to present the results of the non-inferior comparator arm further contributes to the misleading impression created by the piece as a whole that Clindesse therapy is more effective than other treatments indicated for the treatment of bacterial vaginosis, when this has not been shown by substantial evidence or substantial clinical experience.

Minimization of Risk and Limitations to Indication Presentation

Throughout the e-Pharm/alert email effectiveness claims are presented using large, bolded headers with bullets as well as colorful graphics and a colored background. In contrast, all of the risk information, including that Clindesse is only approved for use in non-pregnant women, is relegated to the end of the e-Pharm/alert e-mail after and separated from all the effectiveness claims, blocked in paragraph format, without the use of headers or bullets, with much smaller font. This presentation misleadingly minimizes the risks associated with the use of Clindesse.

Conclusion and Requested Action

For the reasons discussed above, the e-Pharm/alert e-mail overstates and misrepresents the efficacy of Clindesse, presents unsubstantiated superiority and patient compliance claims, and minimizes the risks and limitations to the indication for Clindesse. Accordingly, the e-Pharm alert e-mail misbrands Clindesse in violation of the Federal Food, Drug, and Cosmetic Act (Act). See 21 U.S.C. 352 (a) & (n).

DDMAC requests that KV immediately cease the dissemination of violative promotional materials for Clindesse such as those described above. Please submit a written response to this letter on or before June 1, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Clindesse such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301.796.9877 or 301.796.9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 15021 in addition to the NDA number. We remind you that only written communications are considered official.

[13] As discussed above, these claims overstate the efficacy of Clindesse because they are inconsistent with the efficacy information provided in the Clindesse PI and misrepresent the definition of clinical cure for bacterial vaginosis (BV).

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Clindesse comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Suzanne Berkman, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Suzanne Berkman
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