

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**50-793**

**PHARMACOLOGY REVIEW**

**NDA 50-793****Drug Product:** Clindesse™**Sequence number:** 000**Date of submission:** October 30, 2003**Information to sponsor:** Yes**Sponsor:** KV Pharmaceutical 10888 Metro Court, Maryland Heights, MO 63043**Reviewer:** Owen McMaster, PhD**Division:** Division of Special Pathogen and Immunologic Drug Products**HFD-590****Review completion date:** November 1, 2004**Drug trade name:** Clindesse™**Generic name:** clindamycin phosphate, USP (USAN), clindamycin (INN),**Chemical name:** : 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)**CAS registry number:** 024729-96-2**Molecular formula:** C<sub>18</sub>H<sub>34</sub>ClN<sub>2</sub>O<sub>8</sub>PS**Molecular Weight** 504.96**Related IND's:** IND 3892 (CLEOCIN), \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_**Related NDA's:****NDA 50-200 CLEOCIN®****NDA 50-613 CLEOCIN SP®****NDA 50-441 CLEOCIN PHOSPHATE® sterile solution****NDA 50-537 CLEOCIN® T Topical solution****AADA 62363 CLEOCIN® T Topical solution****NDA 50-600 CLEOCIN® T Topical Lotion****NDA 50-615 CLEOCIN® T Topical Gel****ANDA 62803 CLEOCIN® PHOSPHATE ADD-Vantage (IV-solution)****NDA 50-639 CLEOCIN® PHOSPHATE solution****NDA 50-580 CLEOCIN® vaginal cream**

**Clinical formulation:** Clindesse™ is a semisolid cream containing 2% clindamycin phosphate in addition to edentate disodium, glycerol monoisostearate, lecithin, methylparaben, microcrystalline wax, mineral oil, polyglyceryl-3-oleate, propylparaben, purified water, silicon dioxide and sorbitol solution.

**Indication:** Clindesse™ is indicated for the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, *Corynebacterium* vaginitis or anaerobic vaginitis) in non-pregnant women.

**Administration:** A single applicatorful of Clindesse™ (about 5g) is to be administered once intravaginally.

*Executive Summary*

## I. Recommendations

## A. Recommendation on Approvability

There is no information submitted in this package which would preclude the approval of Clindesse™ for the treatment of bacterial vaginosis.

## B. Recommendation for Nonclinical Studies

No additional toxicology studies are being requested at this time.

## II. Summary of Nonclinical Findings

## A. Brief Overview of Nonclinical Findings

In a 14-day intravaginal toxicology study in rabbits, Clindamycin Vaginal Cream 2% was found to produce congestion, slight edema and reddening of the vagina, but these were less severe than the approved comparator vaginal products.

## III. Administrative

A. Reviewer signature: \_\_\_\_\_

B. Supervisor signature:      Concurrence - \_\_\_\_\_

Non-Concurrence - \_\_\_\_\_

C. cc: list:

HFD-590 Original IND  
HFD-590/PM/CChi  
HFD-590 Division File  
HFD-590/Micro/KSvarna  
HFD-340  
HFD-590/MO/MSinger  
HFD-590/Bio/SJang  
HFD-590/Pharm/OMcMaster  
HFD-590/Chem/DMateka

**Introduction:**

Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7 (R)-hydroxyl group of the parent compound lincomycin. It exerts a potent bacteriostatic effect against streptococci, staphylococci and anaerobic organisms including *Bacterioides fragilis*. It has also been shown to be useful in the treatment of *Pneumocystis carinii* and *Toxoplasma gondii* infections.

Clindamycin binds exclusively to the 50S subunit of bacterial ribosomes and suppresses protein synthesis by altering peptide chain initiation. Plasmid mediated resistance to clindamycin has been found in *B fragilis* and this seems to be due to methylation of bacterial RNA found on the 50 S ribosomal subunit.

The compound was introduced as an orally administered product in 1970 and was indicated for the treatment of staphylococcal and streptococcal infections. Clindamycin hydrochloride capsules contain the hydrated hydrochloride salt of clindamycin. Clindamycin phosphate, the injectable prodrug of clindamycin, was introduced in 1972 for the treatment of serious anaerobic infections. Clindamycin phosphate is also available as a topical therapy for acne vulgaris in the form of Cleocin topical gel, topical lotion or topical solution. Clindesse™ is a semisolid white cream containing clindamycin phosphate at a concentration equivalent to 20 mg clindamycin base per gram.

Bacterial vaginosis (BV) is an inflammation of the vagina associated with increased malodorous vaginal discharge that cannot be attributed to any other cause. The precise etiology of BV remains unknown. In healthy women the dominant vaginal flora is usually *Lactobacillus* spp., which accounts for more than 95% of the organisms present. In BV, *Lactobacillus* spp are still found in 25 to 75% of women, but there is a decrease of 100 to 1000- fold in bacterial counts. *Gardnerella vaginalis* is more prevalent in women with BV and the amount is two to three orders of magnitude higher than in normal women. The overgrowth of *G. vaginalis* is accompanied by similar increases in *Bacterioides* spp., *Peptostreptococcus* spp., *Mycoplasma hominis*, and *Mobiluncus* spp. Clindamycin has shown potent activity against most strains of *Mobiluncus* spp., *Mycoplasma hominis*, and *G. vaginalis* (MIC values less than 1 µg/ml) and strong activity against *Bacterioides* spp. and *Peptostreptococcus* spp. There is good correlation between the in vitro susceptibility data and antibacterial efficacy with clinical efficacy in humans.

#### **Toxicology Study Review:**

**Study title:** Clindamycin vaginal cream 2%, Cleocin vaginal cream 2%, Metronidazole vaginal cream 0.75%, MetroGel vaginal gel 0.75% and vaginal buffer: 14 day irritation study in rabbits.

**Key study findings:** Congestion, slight edema, reddening of the vagina with Clindamycin vaginal cream 2%, less severe than comparator vaginal products.

**Study no:** 02-096

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** February 13, 2003

**GLP compliance:** Non GLP

**QA report:** yes

**Drug lot:** DR139-19

**Formulation/vehicle:** clindamycin, 20mg/g; methylparaben, \_\_\_\_\_ propylparaben  
\_\_\_\_\_

| Group | Treatment                     | Animals |
|-------|-------------------------------|---------|
| 1     | Vaginal Buffer                | 1-4     |
| 2     | Sham                          | 5-8     |
| 3     | Clindamycin vaginal Cream 2 % | 9-12    |
| 4     | Cleocin vaginal cream 2 %     | 13-16   |
| 5     | Metronidazole vaginal cream   | 17-20   |
| 6     | MetroGel vaginal Gel 0.75%    | 21-24   |

Groups of 4 New Zealand White rabbits were treated as outlined above. Animal were treated once daily for 14 consecutive days.

There were no deaths. Soft feces were observed in one clindamycin treated animal between days 7 and 10. Clindamycin-treated animals showed very slight to slight edema in the vaginal tissues. By comparison, metronidazole treated animals showed moderate edema. The vagina was reddened in almost at least 3 of the 4 animals in all groups. Congestion was seen in all animals, as was inflammatory cell infiltrates composed of plasma cells, lymphocytes and heterophils. Edema was also seen in all animals.

In contrast to the generally mild observations in Clindamycin Vaginal Cream treated animals, epithelial degradation and flattening was seen in animals treated with Cleocin Vaginal Cream 2% and Metronidazole Vaginal Cream 0.75 %. In addition, congestion and inflammation were of a higher grade with metronidazole than with Clindamycin Vaginal Cream.

Food consumption was markedly reduced in clindamycin-treated animals between days 2 and 10 (down by as much as 62 % on day 3) and as a result body weight was slightly decreased but by less than 10 %.

In conclusion, Clindamycin Vaginal Cream 2% was found to produce congestion, slight edema and reddening of the vagina, but these were less severe than the approved comparator vaginal products. There is no information submitted in this package which would preclude the approval of Clindesse™ for the treatment of bacterial vaginosis.

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Owen McMaster  
11/29/04 02:42:51 PM  
PHARMACOLOGIST

Steve Hundley  
11/29/04 05:29:07 PM  
PHARMACOLOGIST

Steven Gitterman  
11/29/04 06:08:11 PM  
MEDICAL OFFICER