CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-767

PHARMACOLOGY/TOXICOLOGY REVIEW

Key words: **CLEOCIN® Vaginal Ovule, clindamycin phosphate vaginal suppository, Pharmacia & Upjohn, bacterial vaginosis.**

NDA: 50-767
Reviewer: Owen G. McMaster, Ph.D.
Division: Division of Special Pathogen and Immunologic Drug Products, HFD-590
Completed: August 11, 1999

Sponsor: Pharmacia and Upjohn
7000 Portage Rd
Kalamazoo, Michigan 49001

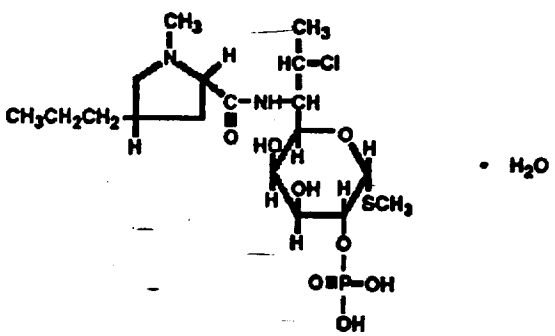
Manufacturer:

Clindamycin phosphate: Pharmacia Upjohn Caribe, Inc.,
Arebico, Puerto Rico, 00612.

CLEOCIN® vaginal ovule: Pharmacia and Upjohn Company
7000 Portage Rd. Kalamazoo, Michigan 49001.

Trade name: CLEOCIN® vaginal ovule.
Generic Names: Clindamycin phosphate USP (USAN), clindamycin (INN),
Code Numbers: PNU-28508E
CAS registry number: 024729-96-2
Chemical Name: Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-*D*-*galacto*-octopyranoside 2-(dihydrogen phosphate)

Structure:



Trademarked product names: DALACIN™ (non-USA), CLEOCIN™ (USA) and SOBELIN™ (Germany)
Molecular formula: $C_{18}H_{34}ClN_2O_8PS$

Molecular Weight 522.98
Physical and Chemical Characteristics: CLEOCIN vaginal ovules are semisolid, white to off-white, 2.5 g suppositories for intravaginal administration.

Related IND's:

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
NDA 50-600 CLEOCIN® T Topical Lotion
NDA 50-615 CLEOCIN® T Topical Gel
NDA 50-639 CLEOCIN® PHOSPHATE solution
NDA 50-580 CLEOCIN® vaginal cream

Indication: CLEOCIN® Vaginal Ovules are indicated for 3-day treatment of bacterial vaginosis in non-pregnant women.

Formulation:

Dosage and administration: The recommended dose is one CLEOCIN® Vaginal ovule, intravaginally per day, preferably at bedtime, for 3 consecutive days

Introduction:

Clindamycin is a semisynthetic antibiotic produced by a 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 *Pneumocyctis carinii* and *Toxoplasma gondii* infections.

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. Cleocin vaginal cream 2% is a semisolid white cream containing 2% clindamycin phosphate and is indicated for bacterial vaginosis.

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 B*acterioides* spp. and *Peptostreptococcus* spp. There is good correlation between the in vitro susceptibility data and antibacterial efficacy with clinical efficacy in humans.

The most common side effects of CLEOCIN® vaginal ovule were vulvovaginal disorders (3.4 %) including vaginal pain (1.9 %) and vaginal moniliasis (1.5 %). Fungal infection was also reported in 1 % of the patients.

The preclinical toxicology of clindamycin phosphate has been studied and reviewed extensively for the previous NDA's listed above. One new study was conducted which addressed the toxic effects of clindamycin [redacted] excipient used in the final drug product.

Toxicology Study Review

U-28508E: 5-day intravaginal irritancy study in ovarectomized female Sprague Dawley rats.
Pathology and Toxicology study number 94-298. July 22, 1994. GLP study. Report # 7227-95-004.

Groups of ovarectomized female rats (Sprague Dawley Crl:CD®BR), 21 rats per group, were treated with 0 (vehicle) or 5 mg of clindamycin phosphate suspended in vaginal suppositories (each weighing approximately 125 mg each) for one to five days. [redacted] Three rats per group were euthanized on days 2, 3, 4, 5, 8 and 12. All remaining rats were euthanized on day 15. Records were kept of mortality, clinical observations, gross necropsy findings and microscopic observations of the vagina and uterus.

No animals died during this study. Animals receiving clindamycin exhibited a moist discharge around the anogenital region with anogenital staining. Inflammation (seen beginning 2 days after initiation of dosing) was observed in the vagina of animals receiving both vehicle and drug and was consistently more severe in vehicle treated animals. Inflammation disappeared by seven days after the cessation of dosing. There was also mild hyperplasia and scattered single cell necrosis in the vaginal epithelium of drug-treated animals. These lesions were first observed three days after the initiation of dosing and were no longer detectable by three days after the cessation of dosing.

Conclusion

Intravaginal administration of clindamycin phosphate, [redacted] hyperplasia and scattered single cell necrosis in the vagina of rats treated for 1 to 5 days. The inflammation seemed to be associated with the vehicle since this effect was more severe in vehicle treated animals. All adverse effects were reversed by 7 days after the cessation of dosing.

Reproductive Toxicology

Studies conducted using CLEOCIN vaginal cream in pregnant women have shown that CLEOCIN vaginal cream is associated with more frequent abnormal labor than women who were not so treated. This finding is noted in the label for the vaginal cream and shall also be included in the label for CLEOCIN® Vaginal Ovule. The following statement shall therefore be added to the proposed labeling for CLEOCIN® Vaginal Ovule.

CLEOCIN Vaginal Cream, 2%, has been studied in pregnant women during the second trimester. In women treated for 7 days, abnormal labor was reported more frequently in patients who received CLEOCIN Vaginal Cream compared to those receiving placebo (1.1% vs. 0.5% of patients, respectively).

Reproductive toxicology studies have detected an increase in the incidence of cleft palates in TUC/ICR mice treated with clindamycin. These experiments were repeated, but there were inconsistencies in the incidences of cleft palate in successive studies.

Table 1. Incidence of litters with cleft palate fetuses in three successive experiments after treatment with subcutaneous clindamycin phosphate.

Dose (mg/kg)	Study 1	Study 2	Study 3
0	0/10	1/8	1/9
100	2/8	2/8	1/10
180	2/10	1/6	0/10

In subsequent studies, cleft palates were seen in control animals and vitamin B administration failed to prevent the occurrence of these cleft palates (some antibiotics are known to produce cleft palates by inducing vitamin B deficiency). No cleft palates were seen in CF1 mice or in any other species.

It was therefore concluded that the cleft palates seen might have been the result of a strain specific effect. Since many of these studies are over 25 years old, the sponsor has agreed to study these effects further and the proposed text of the phase 4 commitment is as follows:

[redacted]

Summary and Conclusions

There are no preclinical findings that would preclude the approval of CLEOCIN vaginal ovule. The potential for abnormal labor has been described in the label. In addition, the sponsor will conduct new preclinical reproductive toxicity studies of clindamycin phosphate.

/S/

Owen G. McMaster, Ph.D.
Reviewer of Pharmacology and Toxicology, DSPIDP

Concurrences:
HFD-590/RAlbrecht
HFD-590/KHastings 8/16/99
Disk:
HFD-590/KHastings
cc:
HFD-590 Original IND
HFD-590/PM/Cchi
HFD-590 Division File
HFD-590/Micro/LGosey
HFD-340
HFD-590/MO/JWinfield
HFD-590/Bio/PColangelo
HFD-590/Pharm/OMcMaster
HFD-590/Chem/DMateka