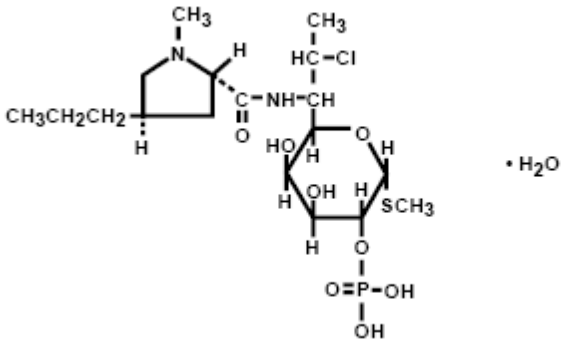
Cleocin® Vaginal Ovules
(clindamycin phosphate vaginal suppositories)

FOR INTRAVAGINAL USE ONLY

DESCRIPTION
Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is 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). The monohydrate form has a molecular weight of 522.98, and the molecular formula is $C_{18}H_{34}ClN_2O_8PS \cdot H_2O$. The structural formula is represented below:



CLEOCIN Vaginal Ovules are semisolid, white to off-white suppositories for intravaginal administration. Each 2.5 g suppository contains clindamycin phosphate equivalent to 100 mg clindamycin in a base consisting of a mixture of glycerides of saturated fatty acids.

CLINICAL PHARMACOLOGY
Mechanism of Action
Clindamycin is an antibacterial drug (See MICROBIOLOGY).

Pharmacokinetics
Systemic absorption of clindamycin was estimated following a once-a-day intravaginal dose of one clindamycin phosphate vaginal suppository (equivalent to 100 mg clindamycin) administered to 11 healthy female volunteers for 3 days. Approximately 30% (range 6% to 70%) of the administered dose was absorbed systemically on day 3 of dosing based on area under the concentration-time curve (AUC). Systemic absorption was estimated using a subtherapeutic 100 mg intravenous dose of clindamycin phosphate as a comparator in the same volunteers. The mean AUC following day 3 of dosing with the suppository was 3.2 µg hr/mL (range 0.42 to 11 µg hr/mL). The C_{max} observed on day 3 of dosing with the suppository averaged 0.27 µg/mL (range 0.03 to 0.67 µg/mL) and was observed about 5 hours after dosing (range 1 to 10 hours). In contrast, the AUC and C_{max} after the single intravenous dose averaged 11 µg hr/mL (range 5.1 to 26 µg hr/mL) and 3.7 µg/mL (range 2.4 to 5.0 µg/mL), respectively. The mean apparent

elimination half-life after dosing with the suppository was 11 hours (range 4 to 35 hours) and is considered to be limited by the absorption rate.

The results from this study showed that systemic exposure to clindamycin (based on AUC) from the suppository was, on average, three-fold lower than that from a single subtherapeutic 100 mg intravenous dose of clindamycin. In addition, the recommended daily and total doses of intravaginal clindamycin suppository are far lower than those typically administered in oral or parenteral clindamycin therapy (100 mg of clindamycin per day for 3 days equivalent to about 30 mg absorbed per day from the ovule relative to 600 to 2700 mg/day for up to 10 days or more, orally or parenterally). The overall systemic exposure to clindamycin from Cleocin Vaginal Ovules is substantially lower than the systemic exposure from therapeutic doses of oral clindamycin hydrochloride (two-fold to 20-fold lower) or parenteral clindamycin phosphate (40-fold to 50-fold lower).

MICROBIOLOGY

Mechanism of Action
Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is predominantly bacteriostatic.

Although clindamycin phosphate is inactive *in vitro,* rapid *in vivo h*ydrolysis converts it to active clindamycin.

Resistance
Resistance to clindamycin is most often caused by modification of the target site on the ribosome, usually by chemical modification of RNA bases or by point mutations in RNA or occasionally in proteins. Cross resistance has been demonstrated between lincosamides, macrolides and streptogramins B in some organisms. Cross resistance has been demonstrated between clindamycin and lincomycin.

Antibacterial Activity
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 pathogens, *Gardnerella vaginalis, Mobiluncus* spp., or *Mycoplasma hominis*, has not been defined.

The following *in vitro* data are available but their clinical significance is unknown. Clindamycin is active in vitro against most isolates of the following organisms reported to be associated with bacterial vaginosis:

- *Bacteroides* spp.
- *Gardnerella vaginalis*
- *Mobiluncus* spp.
- *Mycoplasma hominis*
- *Peptostreptococcus* spp.

INDICATIONS AND USAGE

CLEOCIN Vaginal Ovules are indicated for 3-day treatment of bacterial vaginosis in non-pregnant women. There are no adequate and well-controlled studies of CLEOCIN Vaginal Ovules 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*, *Neisseria gonorrhoeae*, *Candida albicans*, and herpes simplex virus, should be ruled out.

CONTRAINDICATIONS

CLEOCIN Vaginal Ovules are contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin, or any of the components of this vaginal suppository. CLEOCIN Vaginal Ovules are also contraindicated in individuals with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis.

WARNINGS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Orally and parenterally administered clindamycin has been associated with severe colitis, which may end fatally. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of orally and parenterally administered clindamycin, as well as with topical (dermal and vaginal) formulations of clindamycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of CLEOCIN Vaginal Ovules, because approximately 30% of the clindamycin dose is systemically absorbed from the vagina.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridioides difficile* is a primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridioides difficile* colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.

PRECAUTIONS

General

The use of CLEOCIN Vaginal Ovules may result in the overgrowth of nonsusceptible organisms in the vagina. In clinical studies using CLEOCIN Vaginal Ovules, treatment-related moniliasis was reported in 2.7% and vaginitis in 3.6% of 589 nonpregnant women. Moniliasis, as reported here, includes the terms: vaginal or nonvaginal moniliasis and fungal infection. Vaginitis includes the terms: vulvovaginal disorder, vaginal discharge, and vaginitis/vaginal infection.

Information for the Patient

The patient should be instructed not to engage in vaginal intercourse or use other vaginal products (such as tampons or douches) during treatment with this product.

The patient should also be advised that these suppositories use an oleaginous base that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, the use of such products within 72 hours following treatment with CLEOCIN Vaginal Ovules is not recommended.

Drug Interactions

Systemic clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative. Fertility studies in rats treated orally with up to 300 mg/kg/day (31 times the human exposure based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic effects

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters, has not been associated with an increased frequency of congenital abnormalities.

Clindamycin vaginal ovules should be used during the first trimester of pregnancy only if clearly needed and the benefits outweigh the risks. There are no adequate and well-controlled studies of CLEOCIN Vaginal Ovules in pregnant women during the first trimester of pregnancy.

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).

Reproduction studies have been performed in rats and mice using oral and parenteral doses of clindamycin up to 600 mg/kg/day (62 and 25 times, respectively, the maximum human dose based on body surface area) and have revealed no evidence of harm to the fetus due to

clindamycin. Cleft palates were observed in fetuses from one mouse strain treated intraperitoneally with clindamycin at 200 mg/kg/day (about 10 times the recommended dose based on body surface area conversions). Since this effect was not observed in other mouse strains or in other species, the effect may be strain specific.

Nursing Mothers

Limited published data based on breast milk sampling reports that clindamycin appears in human breast milk in the range of less than 0.5 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. It is not known if clindamycin is excreted in human breast milk following the use of vaginally administered clindamycin phosphate.

Clindamycin has the potential to cause adverse effects on the breast-fed infant's gastrointestinal flora. If clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. Monitor the breast-fed infant for possible adverse effects on the gastrointestinal flora, such as diarrhea, candidiasis (thrush, diaper rash) or rarely, blood in the stool indicating possible antibiotic-associated colitis.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breast-fed child from clindamycin or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of CLEOCIN Vaginal Ovules in the treatment of bacterial vaginosis in post-menarchal females have been established on the extrapolation of clinical trial data from adult women. When a post-menarchal adolescent presents to a health professional with bacterial vaginosis symptoms, a careful evaluation for sexually transmitted diseases and other risk factors for bacterial vaginosis should be considered. The safety and efficacy of CLEOCIN Vaginal Ovules in pre-menarchal females have not been established.

Geriatric Use

Clinical studies of CLEOCIN Vaginal Ovules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Clinical Trials

In clinical trials, 3 (0.5%) of 589 nonpregnant women who received treatment with CLEOCIN Vaginal Ovules discontinued therapy due to drug-related adverse events. Adverse events judged to have a reasonable possibility of having been caused by clindamycin phosphate vaginal suppositories were reported for 10.5% of patients. Events reported by 1% or more of patients receiving CLEOCIN Vaginal Ovules were as follows:

Urogenital system: Vulvovaginal disorder (3.4%), vaginal pain (1.9%), and vaginal moniliasis (1.5%).

Body as a whole: Fungal infection (1.0%).

Other events reported by <1% of patients included:
Urogenital system: Menstrual disorder, dysuria, pyelonephritis, vaginal discharge, and vaginitis/vaginal infection.
Body as a whole: Abdominal cramps, localized abdominal pain, fever, flank pain, generalized pain, headache, localized edema, and moniliasis.
Digestive system: Diarrhea, nausea, and vomiting.
Skin: Nonapplication-site pruritis, rash, application-site pain, and application-site pruritis.

Other clindamycin formulations:

The overall systemic exposure to clindamycin from CLEOCIN Vaginal Ovules is substantially lower than the systemic exposure from therapeutic doses of oral clindamycin hydrochloride (two-fold to 20-fold lower) or parenteral clindamycin phosphate (40-fold to 50-fold lower). (See CLINICAL PHARMACOLOGY.) Although these lower levels of exposure are less likely to produce the common reactions seen with oral or parenteral clindamycin, the possibility of these and other reactions cannot be excluded.

The following adverse reactions and altered laboratory tests have been reported with the **oral or parenteral** use of clindamycin and may also occur following administration of CLEOCIN Vaginal Ovules:

Infections and Infestations: *Clostridioides difficile* colitis

Gastrointestinal: Abdominal pain, esophagitis, nausea, vomiting, diarrhea, and pseudomembranous colitis. (See WARNINGS.)

Hematopoietic: Transient neutropenia (leukopenia), eosinophilia, agranulocytosis, and thrombocytopenia have been reported. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of these reports.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Cases of Acute Generalized Exanthematous Pustulosis (AGEP), erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued.

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Musculoskeletal: Cases of polyarthritis have been reported.

Renal: Acute kidney injury

Immune System: Drug reaction with eosinophilia and systemic symptoms (DRESS) cases have been reported.

There have been reports of pseudomembranous colitis following the administration of clindamycin vaginal cream.

OVERDOSAGE

Vaginally applied clindamycin phosphate contained in CLEOCIN Vaginal Ovules could be absorbed in sufficient amounts to produce systemic effects. (See WARNINGS and ADVERSE REACTIONS.)

DOSAGE AND ADMINISTRATION

The recommended dose is one CLEOCIN Vaginal Ovule (containing clindamycin phosphate equivalent to 100 mg clindamycin per 2.5 g suppository) intravaginally per day, preferably at bedtime, for 3 consecutive days.

HOW SUPPLIED

CLEOCIN Vaginal Ovules are supplied as follows:
Carton of three suppositories with one applicator NDC 0009-7667-01

Important Information: Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F) [see USP Controlled Room Temperature].

Caution: Avoid heat over 30°C (86°F). Avoid high humidity. See end of carton for the lot number and expiration date.

Rx only

This product's labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Pfizer

Distributed by
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New York, NY 10017

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Cleocin® Vaginal Ovules
(clindamycin phosphate vaginal suppositories)

DIRECTIONS FOR USE

How do I use CLEOCIN Vaginal Ovules?
For vaginal use only. Do not take by mouth.

Use one CLEOCIN Vaginal Ovule daily, preferably at bedtime, for 3 days in a row.

Do not use this product if the foiled pouches containing vaginal ovules are torn, opened, or incompletely sealed.

Read the full directions below before using.

Insertion with the applicator:
1. Remove the vaginal ovule from its packaging (See Figure 1).

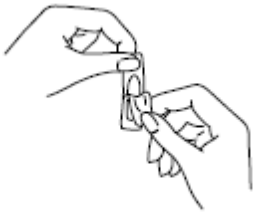


Figure 1

2. Pull back the plunger about an inch and place the vaginal ovule in the wider end of the applicator barrel (See Figure 2).

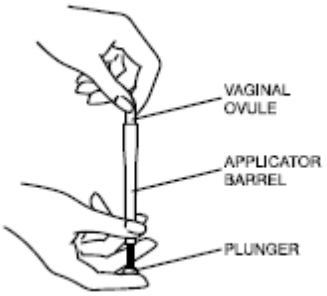


Figure 2

3. Hold the applicator as shown and gently insert the end of the applicator into the vagina as far as it will go comfortably. This can be done while lying on your back with your knees bent (as shown in Figure 3), or while standing with your feet apart and your knees bent.

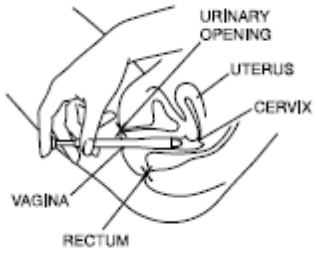


Figure 3

4. While holding the barrel of the applicator in place, push the plunger in until it stops to release the vaginal ovule. Remove the applicator from the vagina.
5. Clean the applicator after each use. Pull the two pieces apart and wash them with soap and warm water. Rinse well and dry. Put the two pieces back together and store in a clean, dry place.
6. Once inside the vagina, the ovule melts. Lie down as soon as possible. This will keep leakage to a minimum.
7. Repeat steps 1 through 6, before bedtime, for the next 2 days.

Insertion without the applicator:
1. Remove the vaginal ovule from its packaging (See Figure 1).
2. Holding the ovule with your thumb and a finger, insert it into the vagina.
3. Using your finger, gently push the ovule into the vagina as far as it will comfortably go.
4. Once inside the vagina, the ovule melts. Lie down as soon as possible. This will keep leakage to a minimum.
5. Repeat steps 1 through 4, before bedtime, for the next 2 days.

STORAGE CONDITIONS:
Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F) [see USP Controlled Room Temperature].
Caution: Avoid heat over 30°C (86°F). Avoid high humidity. See end of carton for the lot number and expiration date.

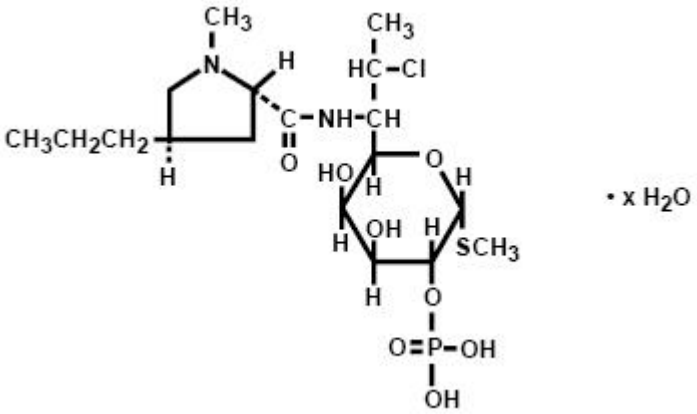
LAB-0649-1.0
Revised December 2012

Cleocin®
clindamycin phosphate vaginal cream, USP

FOR INTRAVAGINAL USE ONLY
NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE

DESCRIPTION

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is 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). It has a molecular weight of 504.96, and the molecular formula is $C_{18}H_{34}ClN_2O_8PS$. The structural formula is represented below:



CLEOCIN Vaginal Cream 2%, is a semi-solid, white cream, which contains 2% clindamycin phosphate, USP, at a concentration equivalent to 20 mg clindamycin per gram. The pH of the cream is between 3.0 and 6.0. The cream also contains benzyl alcohol, cetostearyl alcohol, mixed fatty acid esters, mineral oil, polysorbate 60, propylene glycol, purified water, sorbitan monostearate, and stearic acid.

Each applicatorful of 5 grams of vaginal cream contains approximately 100 mg of clindamycin phosphate.

CLINICAL PHARMACOLOGY

Mechanism of Action

Clindamycin is an antibacterial drug (See MICROBIOLOGY).

Pharmacokinetics

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% (range 0.6% to 11%) of the administered dose was absorbed systemically. The peak serum clindamycin concentration observed on the first day averaged 18 ng/mL (range 4

to 47 ng/mL) and on day 7 it averaged 25 ng/mL (range 6 to 61 ng/mL). These peak concentrations were attained approximately 10 hours post-dosing (range 4–24 hours).

Following a once a day intravaginal dose of 100 mg of clindamycin phosphate vaginal cream 2%, administered for 7 consecutive days to 5 women with bacterial vaginosis, absorption was slower and less variable than that observed in healthy females. Approximately 5% (range 2% to 8%) of the dose was absorbed systemically. The peak serum clindamycin concentration observed on the first day averaged 13 ng/mL (range 6 to 34 ng/mL) and on day 7 it averaged 16 ng/mL (range 7 to 26 ng/mL). These peak concentrations were attained approximately 14 hours post-dosing (range 4–24 hours).

There was little or no systemic accumulation of clindamycin after repeated vaginal dosing of clindamycin phosphate vaginal cream 2%. The systemic half-life was 1.5 to 2.6 hours.

MICROBIOLOGY

Mechanism of Action

Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is predominantly bacteriostatic. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts it to active clindamycin.

Resistance

Resistance to clindamycin is most often caused by modification of the target site on the ribosome, usually by chemical modification of RNA bases by point mutations in RNA or occasionally in proteins. Cross resistance has been demonstrated between lincosamides, macrolides and streptogramins B in some organisms. Cross resistance has been demonstrated between clindamycin and lincomycin.

Antibacterial Activity

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 pathogens, *Gardnerella vaginalis, Mobiluncus* spp., or *Mycoplasma hominis*, has not been defined.

The following *in vitro* data are available but their clinical significance is unknown. Clindamycin is active *in vitro* against most isolates of the following organisms reported to be associated with bacterial vaginosis:

- *Bacteroides* spp.
- *Gardnerella vaginalis*
- *Mobiluncus* spp.
- *Mycoplasma hominis*
- *Peptostreptococcus* spp.

INDICATIONS AND USAGE

CLEOCIN Vaginal Cream 2%, is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis). CLEOCIN Vaginal Cream 2%, can be used to treat non-pregnant women and pregnant women during the second and third trimester. (See CLINICAL STUDIES.)

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.

CONTRAINDICATIONS

CLEOCIN Vaginal Cream 2%, is contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin, or any of the components of this vaginal cream. CLEOCIN Vaginal Cream 2%, is also contraindicated in individuals with a history of regional enteritis, ulcerative colitis, or a history of "antibiotic-associated" colitis.

WARNINGS

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of orally and parenterally administered clindamycin, as well as with topical (dermal and vaginal) formulations of clindamycin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of clindamycin, even when administered by the vaginal route, because approximately 5% of the clindamycin dose is systemically absorbed from the vagina.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridioides difficile* is a primary cause of "antibiotic-associated" colitis.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridioides difficile* colitis.

Onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.

PRECAUTIONS

General

CLEOCIN Vaginal Cream 2%, contains ingredients that will cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

The use of CLEOCIN Vaginal Cream 2% may result in the overgrowth of nonsusceptible organisms in the vagina. In clinical studies involving 600 non-pregnant women who received treatment for 3 days, *Candida albicans* was detected, either symptomatically or by culture, in 8.8% of patients. In 9% of the patients, vaginitis was recorded. In clinical studies involving 1325 non-pregnant women who received treatment for 7 days, *Candida albicans* was detected, either symptomatically or by culture, in 10.5% of patients. Vaginitis was recorded in 10.7% of the patients. In 180 pregnant women who received treatment for 7 days, *Candida albicans* was detected, either symptomatically or by culture, in 13.3% of patients. In 7.2% of the patients, vaginitis was recorded. *Candida albicans,* as reported here, includes the terms: vaginal moniliasis and moniliasis (body as a whole). Vaginitis includes the terms: vulvovaginal disorder, vulvovaginitis, vaginal discharge, trichomonal vaginitis, and vaginitis.

Information for the Patient:

The patient should be instructed not to engage in vaginal intercourse, or use other vaginal products (such as tampons or douches) during treatment with this product.

The patient should also be advised that this cream contains mineral oil that may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, use of such products within 72 hours following treatment with CLEOCIN Vaginal Cream 2%, is not recommended.

Drug Interactions

Systemic clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative. Fertility studies in rats treated orally with up to 300 mg/kg/day (31 times the human exposure based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: *Teratogenic effects*
In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters, has not been associated with an increased frequency of congenital abnormalities.

Clindamycin vaginal cream should be used during the first trimester of pregnancy only if clearly needed and the benefits outweigh the risks. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

CLEOCIN Vaginal Cream 2% has been studied in pregnant women during the second trimester. In women treated for seven days, abnormal labor was reported in 1.1% of patients who received clindamycin vaginal cream 2% compared with 0.5% of patients who received placebo.

Reproduction studies have been performed in rats and mice using oral and parenteral doses of clindamycin up to 600 mg/kg/day (62 and 25 times, respectively, the maximum human exposure based on body surface area) and have revealed no evidence of harm to the fetus due to clindamycin. Cleft palates were observed in fetuses from one mouse strain treated intraperitoneally with clindamycin at 200 mg/kg/day (about 10 times the recommended dose based on body surface area conversions). Since this effect was not observed in other mouse strains or in other species, the effect may be strain specific.

Nursing Mothers
Limited published data based on breast milk sampling reports that clindamycin appears in human breast milk in the range of less than 0.5 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. It is not known if clindamycin is excreted in human breast milk following the use of vaginally administered clindamycin phosphate.

Clindamycin has the potential to cause adverse effects on the breast-fed infant's gastrointestinal flora. If clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. Monitor the breast-fed infant for possible adverse effects on the gastrointestinal flora, such as diarrhea, candidiasis (thrush, diaper rash) or rarely, blood in the stool indicating possible antibiotic-associated colitis.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breast-fed child from clindamycin or from the underlying maternal condition.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies for CLEOCIN Vaginal Cream 2% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger

subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

Clinical trials

Non-pregnant Women: In clinical trials involving non-pregnant women, 1.8% of 600 patients who received treatment with CLEOCIN Vaginal Cream 2% for 3 days and 2.7% of 1325 patients who received treatment for 7 days discontinued therapy due to drug-related adverse events. Medical events judged to be related, probably related, possibly related, or of unknown relationship to vaginally administered clindamycin phosphate vaginal cream 2%, were reported for 20.7% of the patients receiving treatment for 3 days and 21.3% of the patients receiving treatment for 7 days. Events occurring in ≥1% of patients receiving clindamycin phosphate vaginal cream 2% are shown in Table 1.

TABLE 1 – Events Occurring in ≥1% of Non-pregnant Patients Receiving Clindamycin Phosphate Vaginal Cream 2%

Event	CLEOCIN Vaginal Cream	
	3 Day n=600	7 Day n=1325
Urogenital		
Vaginal moniliasis	7.7	10.4
Vulvovaginitis	6.0	4.4
Vulvovaginal disorder	3.2	5.3
Trichomonal vaginitis	0	1.3
Body as a Whole		
Moniliasis (body)	1.3	0.2

Other events occurring in <1% of the clindamycin vaginal cream 2% groups include:
Urogenital system: vaginal discharge, metrorrhagia, urinary tract infection, endometriosis, menstrual disorder, vaginitis/vaginal infection, and vaginal pain.
Body as a whole: localized abdominal pain, generalized abdominal pain, abdominal cramps, halitosis, headache, bacterial infection, inflammatory swelling, allergic reaction, and fungal infection.
Digestive system: nausea, vomiting, constipation, dyspepsia, flatulence, diarrhea, and gastrointestinal disorder.
Endocrine system: hyperthyroidism.
Central nervous system: dizziness and vertigo.
Respiratory system: epistaxis.
Skin: pruritus (non-application site), moniliasis, rash, maculopapular rash, erythema, and urticaria.
Special senses: taste perversion.

Pregnant Women: In a clinical trial involving pregnant women during the second trimester, 1.7% of 180 patients who received treatment for 7 days discontinued therapy due to drug-related adverse events. Medical events judged to be related, probably related,

possibly related, or of unknown relationship to vaginally administered clindamycin phosphate vaginal cream 2%, were reported for 22.8% of pregnant patients. Events occurring in ≥1% of patients receiving either clindamycin phosphate vaginal cream 2% or placebo are shown in Table 2.

TABLE 2 - Events Occurring in ≥1% of Pregnant Patients Receiving Clindamycin Phosphate Vaginal Cream 2% or Placebo

Event	CLEOCIN Vaginal Cream 7 DAY n=180	Placebo 7 Day n=184
Urogenital		
Vaginal moniliasis	13.3	7.1
Vulvovaginal disorder	6.7	7.1
Abnormal labor	1.1	0.5
Body as a Whole		
Fungal infection	1.7	0
Skin		
Pruritus, non-application site	1.1	0

Other events occurring in <1% of the clindamycin vaginal cream 2% group include:
Urogenital system: dysuria, metrorrhagia, vaginal pain, and trichomonal vaginitis.
Body as a whole: upper respiratory infection.
Skin: pruritus (topical application site) and erythema.

Post-marketing Experience
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In the post-marketing period, there have been case reports of pseudomembranous colitis with the use of clindamycin phosphate vaginal cream.

Other clindamycin formulations:

Clindamycin vaginal cream affords minimal peak serum levels and systemic exposure (AUCs) of clindamycin compared to 100 mg oral clindamycin dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral clindamycin, the possibility of these and other reactions cannot be excluded presently. Data from well-controlled trials directly comparing clindamycin administered orally to clindamycin administered vaginally are not available.

The following adverse reactions and altered laboratory tests have been reported with the **oral or parenteral** use of clindamycin:

Infections and Infestations: Clostridioides difficile colitis

Gastrointestinal: Abdominal pain, esophagitis, nausea, vomiting, diarrhea, and pseudomembranous colitis. (See WARNINGS.)

Hematopoietic: Transient neutropenia (leukopenia), eosinophilia, agranulocytosis, and thrombocytopenia have been reported. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of these reports.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Cases of Acute Generalized Exanthematous Pustulosis (AGEP), erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued.

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Musculoskeletal: Cases of polyarthritis have been reported.

Renal: Acute kidney injury

Immune System: Drug reaction with eosinophilia and systemic symptoms (DRESS) cases have been reported.

OVERDOSAGE

Vaginally applied clindamycin phosphate vaginal cream 2% could be absorbed in sufficient amounts to produce systemic effects. (See WARNINGS.)

DOSAGE AND ADMINISTRATION

The recommended dose is one applicatorful of clindamycin phosphate vaginal cream 2%, (5 grams containing approximately 100 mg of clindamycin phosphate) intravaginally, preferably at bedtime, for 3 or 7 consecutive days in non-pregnant patients and for 7 consecutive days in pregnant patients. (See CLINICAL STUDIES.)

HOW SUPPLIED

CLEOCIN Vaginal Cream 2%, (clindamycin phosphate vaginal cream) is supplied as follows:

40 g tube (with 7 disposable applicators) NDC 0009-3448-01

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP]. Protect from freezing.

CLINICAL STUDIES

In two clinical studies involving 674 evaluable non-pregnant women with bacterial vaginosis comparing CLEOCIN Vaginal Cream 2% for 3 or 7 days, the clinical cure

rates, determined at 1 month posttherapy, ranged from 72% to 81% for the 3-day treatment and 84% to 86% for the 7-day treatment.

	CLEOCIN 3 Day		CLEOCIN 7 Day	
US Study	94/131	72%	110/128	86%
European Study	161/199	81%	181/216	84%

In a clinical study involving 249 evaluable pregnant patients in the second and third trimester treated for 7 days, the clinical cure rate, determined at 1 month posttherapy, was 60% (77/129) in the clindamycin arm and 9% (11/120) for the vehicle arm. The determination of clinical cure was based on the absence of a “fishy” amine odor when the vaginal discharge was mixed with a 10% KOH solution and the absence of clue cells on microscopic examination.

Rx only

This product’s labeling may have been updated. For the most recent prescribing information, please visit www.pfizer.com.

Distributed by
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A subsidiary of Pfizer Inc.
New York, NY 10017

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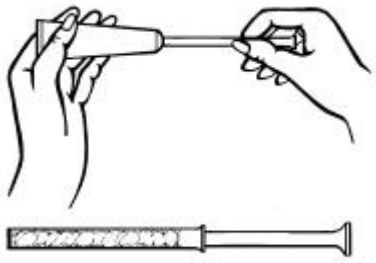
DIRECTIONS FOR USE

Disposable plastic applicators are provided with this package. They are designed to allow proper vaginal administration of the cream.

Remove cap from cream tube. Screw a plastic applicator on the threaded end of the tube.

Rolling tube from the bottom, squeeze gently and force the medication into the applicator. The applicator is filled when the plunger reaches its predetermined stopping point.

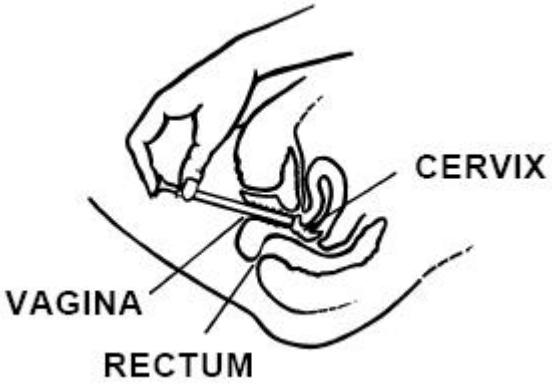
Unscrew the applicator from the tube and replace the cap.



While lying on your back, firmly grasp the applicator barrel and insert into vagina as far as possible without causing discomfort.

Slowly push the plunger until it stops.

Carefully withdraw applicator from vagina, and discard applicator.



REMEMBER TO APPLY ONE APPLICATORFUL EACH NIGHT BEFORE BEDTIME, OR AS PRESCRIBED BY YOUR DOCTOR.

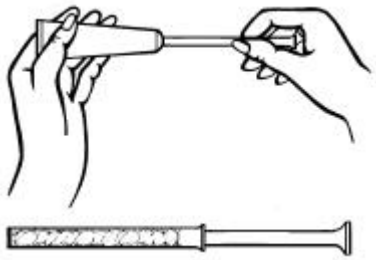
INSTRUCCIONES PARA LA PACIENTE

Este envase contiene aplicadores de plástico desechables. Los aplicadores están diseñados para la administración apropiada de la crema en la vagina.

Remueva la tapa del tubo de crema y enrosque el aplicador de plástico al tubo.

Exprima el tubo suavemente desde el extremo inferior y fuerce el medicamento al aplicador. El aplicador estará lleno cuando el émbolo llega a su máxima longitud.

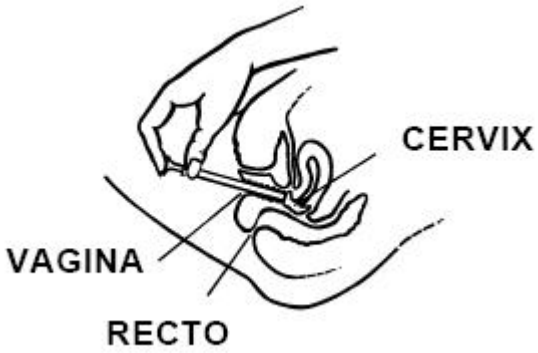
Desenrosque el aplicador del tubo y vuelva a poner la tapa.



Acuéstese de espalda y agarrando firmemente el aplicador, introdúzcalo en la vagina tanto como sea posible sin causar molestias.

Empuje lentamente el émbolo hasta que se detenga.

Saque el aplicador cuidadosamente de la vagina y descártelo.



RECUERDE APLICARSE UN APLICADOR LLENO TODAS LAS NOCHES AL ACOSTARSE, O DE ACUERDO CON LAS INDICACIONES DE SU MEDICO.

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