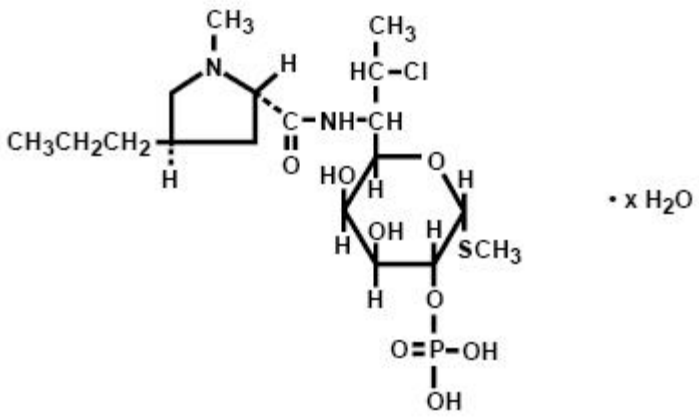
DALACIN V Vaginal Cream (Clindamycin Phosphate)

1. NAME OF THE DRUG PRODUCT
DALACIN V Vaginal Cream 2%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
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:



Clindamycin 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.

3. PHARMACEUTICAL FORM
Vaginal cream.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
DALACIN V Vaginal Cream 2% is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, non-specific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis).

DALACIN V Vaginal Cream can be used to treat non-pregnant women and pregnant women during their second and third trimesters.(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.

4.2. Posology and method of administration
The recommended dose is one applicatorful of clindamycin 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]**)

4.3. Contraindications
DALACIN V vaginal cream 2%, is contraindicated in individuals with a history of hypersensitivity to clindamycin, lincomycin or any of the components of this vaginal cream. Clindamycin vaginal cream 2%, is also contraindicated in individuals with regional enteritis, ulcerative colitis, or a history of “antibiotic-associated colitis”.

4.4. Special warnings and precautions for use

General
DALACIN V 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 Clindamycin 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 DALACIN V Vaginal Cream 2%, is not recommended.

Pediatric use
Safety and efficacy in pediatric patients have not been established.

4.5. Interaction with other medicinal products and other forms of interaction
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.

4.6. Fertility, pregnancy and lactation
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.

DALACIN V 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 breastfed child from clindamycin or from the underlying maternal condition.

4.7. Effects on ability to drive and use machines
The effect of clindamycin on the ability to drive or operate machinery has not been systematically evaluated.

4.8. Undesirable effects

Clinical trials

Non-pregnant Women: In clinical trials involving non-pregnant women, 1.8% of 600 patients who received treatment with DALACIN V 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	DALACIN V 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	DALACIN V 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 Section **[4.4. Special warnings and precautions for use]**).

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.

4.9. Overdose
Vaginally applied clindamycin phosphate vaginal cream 2% could be absorbed in sufficient amounts to produce systemic effects. (See Section **[4.4. Special warnings and precautions for use]**)

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics properties
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 due to 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 *in vitro* 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 section **[4.1. Therapeutic indications]**); 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 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.

5.2. Pharmacokinetic properties

Mechanism of Action
Clindamycin is an antibacterial drug (See Section **[5.1. Pharmacodynamics properties]**).

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.

GERIATRIC USE
Clinical studies for DALACIN V 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.

5.3. Preclinical safety data

Carcinogenesis
Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential.

Mutagenesis
Genotoxicity tests performed included a rat micronucleus test and an Ames test. Both tests were negative.

Impairment of Fertility
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.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients
Excipients:
Purified water
Mineral oil USP-viscosity 180

Stearic acid external use only
Propylene glycol USP
Benzyl alcohol
Cetostearyl alcohol NF
Sorbitan monostearate
Polysorbate 60 (food grade)
Cetyl palmitate (cetyl ester wax)

6.2. Incompatibilities
Not available

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store below 30°C.
Protect from heat, sunlight and freezing.

6.5. Nature and contents of container and special equipment for use/administration or Implantation
DALACIN V vaginal Cream 2% (clindamycin phosphate) is supplied in 20 g tube with 3 disposable applicators.

6.6 Special precautions for disposal
No special requirements.

6.7 Drug Product Specifications
USP Specs.

7. REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER
Marketed by
Pfizer Pakistan Limited
B-2, S.I.T.E., Karachi

Name of Manufacturing site	Address of site	Manufacturing step
Pfizer Pakistan Limited	B-2, S.I.T.E., Karachi, Pakistan	Manufacturing, Packaging & Batch Release

8. REGISTRATION / MARKETING AUTHORIZATION NUMBER

018574

9. DATE FROM WHICH MARKETING IS AUTHORIZED

17-March-1996

10. DATE OF REVISION OF THE TEXT

12-March-2021

CLINICAL STUDIES

In two clinical studies involving 674 evaluable non-pregnant women with bacterial vaginosis comparing DALACIN V 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.

	DALACIN V 3 Day		DALACIN V 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.

Dalacin-V/LPD/PK-01
According to approved USPI dated: May 26, 2022 & approved information in Pakistan

Please visit our website ***www.pfizerpro.com.pk*** *for latest version of Product leaflet.*

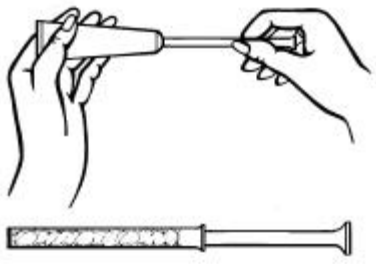
DIRECTIONS FOR USE

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.

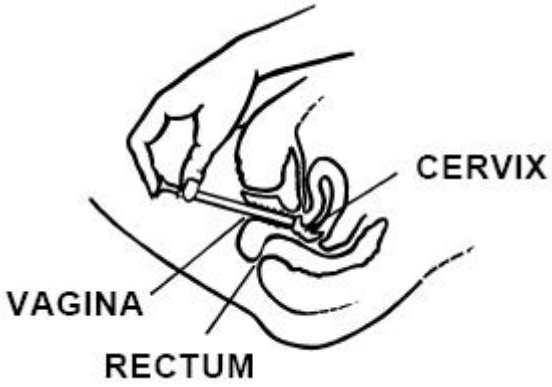
Unscrew the applicator from the tube and replace the cap.



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.