DALACIN V Vaginal Cream
(Clindamycin Phosphate)

1. NAME OF THE MEDICINAL PRODUCT
DALACIN V Vaginal Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
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.

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. 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%[1-9] 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.[13,14]

4.2. POSOLOGY AND METHOD OF ADMINISTRATION
DALACIN V Vaginal Cream:
The recommended dose is one applicatorful of clindamycin vaginal cream 2% intravaginally, preferably at bedtime, for three or seven consecutive days.[3-9]

4.3. CONTRAINDICATIONS
Clindamycin vaginal cream is contraindicated in patients with a history of hypersensitivity to clindamycin, lincomycin or any of the components of these products. Clindamycin vaginal cream[25] is also contraindicated in individuals with a history of antibiotic-associated colitis.[34,35]

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The use of clindamycin vaginal products[3-12] may result in the overgrowth of non-susceptible organisms, particularly yeasts.

Orally and parenterally administered clindamycin, similar to virtually all other antibiotics, has been associated with diarrhea, and in some cases, antibiotic-associated colitis. If significant or prolonged diarrhea occurs during the use of any clindamycin vaginal product, the drug should be discontinued and appropriate diagnostic procedures and treatment provided as necessary.

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

Clindamycin vaginal cream contains ingredients which may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms. Therefore, use of these products during treatment with clindamycin vaginal cream 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.[23,24,40] Therefore, it should be used with caution in patients receiving such agents.

4.6. FERTILITY, PREGNANCY AND LACTATION

Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin,[38] except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.[39]

In clinical trials, the use of clindamycin vaginal products[11,12,13,14] in pregnant women in their second and third trimesters, and systemically administered clindamycin during their second and third trimesters,[17,18,19] has not been associated with an increased frequency of congenital abnormalities.

If clindamycin vaginal cream is used during the second or third trimester, the possibility of fetal harm appears remote.

Clindamycin vaginal cream should be used during the first trimester of pregnancy only if clearly needed.

There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.[39]

Use in Nursing Mothers
It is not known if clindamycin is excreted in human breast milk following the use of vaginally administered clindamycin vaginal cream. Clindamycin has been reported to appear in human breast milk in ranges from <0.5 to 3.8 µg/mL following systemic use.[20,54,55,56]

Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. If clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. 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.[56]

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

DALACIN V Vaginal Cream:

The safety of clindamycin vaginal cream was evaluated in both non-pregnant patients[3-9,21,22] and patients during their second and third trimesters of pregnancy.[13,14]

Adverse Drug Reactions Table for Clindamycin Vaginal Cream[41,42]						
System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10,000 to <1/1000**	**Very Rare <1/10,000**	**Frequency Not Known (cannot be estimated from available data)**
Infections and infestations		Fungal infection, candida infection[35]	Bacterial infection			Skin candida[35]
Immune system disorders			Hypersensitivity			
Endocrine disorders						Hyperthyroidism
Nervous system disorders		Headache, dizziness, dysgeusia				
Ear and labyrinth disorders			Vertigo			
Respiratory, thoracic and mediastinal disorders		Upper respiratory infection	Epistaxis			
Gastrointestinal disorders		Abdominal pain, constipation, diarrhoea, nausea, vomiting	Abdominal distension, flatulence, breath odour			Pseudomembranous colitis*[37], gastrointestinal disorder, dyspepsia
Skin and subcutaneous tissue disorders		Pruritus (non-applicable site), rash	Urticaria, erythema			Rash maculopapular
Musculoskeletal and connective tissue disorders		Back pain				
Renal and urinary disorders		Urinary tract infection, glycosuria, proteinuria	Dysuria			
Pregnancy, puerperium and perinatal conditions		Abnormal labour				

Adverse Drug Reactions Table for Clindamycin Vaginal Cream[41,42]						
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Reproductive system and breast disorders	vulvovaginal candidiasis[35]	Vulvovaginitis, vulvovaginal disorder, menstrual disorder, vulvovaginal pain, metrorrhagia, vaginal discharge	Vulvovaginitis trichomonal, vaginal infection, pelvic pain			Endometriosis
General disorders and administration site conditions						Inflammation, pain
Investigations			Microbiology test abnormal			

* ADRs identified post-marketing

4.9. OVERDOSE

Vaginally applied clindamycin phosphate contained in clindamycin vaginal cream[26] can be absorbed in sufficient amounts to produce systemic effects.[34] In the event of overdosage, general symptomatic and supportive measures are indicated as required.[35]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis at the level of the bacterial ribosome. The antibiotic binds preferentially to the 50S ribosomal subunit and affects the translation process.[28,29] Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.[43,53]

Clindamycin, like most protein synthesis inhibitors, is predominantly bacteriostatic and efficacy is associated with the length of time the concentration of active ingredient remains above the MIC of the infecting organism.[44,53]

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.[45,46,53]

Clindamycin is active *in vitro* against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:[28,30,47,53]

- *Bacteroides* spp.
- *Gardnerella vaginalis*

- *Mobiluncus* spp.
- *Mycoplasma hominis*
- *Peptostreptococcus* spp.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis and to guide treatment.[48] Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis* and *Mobiluncus* spp. has not been defined. Methods for determining the susceptibility of *Bacteroides* spp. and Gram-positive anaerobic cocci, as well as *Mycoplasma* spp. have been described by the Clinical and Laboratory Standards Institute (CLSI) and clindamycin susceptibility breakpoints for Gram-negative and Gram-positive anaerobes have been published by both EUCAST and CLSI.[49,50,51,52] Clinical isolates that test susceptible to clindamycin and resistant to erythromycin should also be tested for inducible clindamycin resistance using the D-test. However, the breakpoints are intended to guide systemic, rather than localized, antibiotic treatment.[53]

5.2. PHARMACOKINETIC PROPERTIES

Clindamycin vaginal cream:
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 4% (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 4% (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.[15]

GERIATRIC USE
Clinical studies for clindamycin phosphate vaginal cream 2% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.[26]

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.[31,32]

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.[33]

In oral embryo-fetal development studies in rats and subcutaneous embryo-fetal development studies in rats and rabbits, no developmental toxicity was observed except at doses that produced maternal toxicity.[36]

6. PHARMACEUTICAL PARTICULARS

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 monostreate
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 CONTENT OF CONTAINER
DALACIN V vaginal Cream 2% (clindamycin phosphate) is supplied in 20 g tube with 3 disposable applicators.

Dalacin-V/LPD/PK-06
According to CDS V 10 dated: March 14, 2019; Supersedes CDS V 9 dated: June 13, 2018

Marketed By

Pfizer Pakistan Limited

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

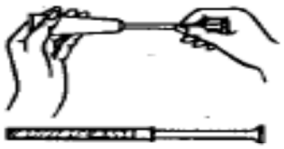
DIRECTIONS FOR USE

Three 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.

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