AUSTRALIAN PRODUCT INFORMATION - DALACIN® V Cream 2% (Clindamycin phosphate) Intravaginal Cream

1. NAME OF THE MEDICINE

Clindamycin phosphate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DALACIN V Cream 2% contains the equivalent of 2% (20 mg/g) free clindamycin as a water soluble ester of clindamycin and phosphoric acid (clindamycin phosphate). Each unit dose of DALACIN V Cream 2% (approximately 5 grams) represents 100 mg of clindamycin.

For the full list of excipients, see section 6.1, List of Excipients.

3. PHARMACEUTICAL FORM

Intravaginal cream.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DALACIN V Cream 2% is indicated for the treatment of symptomatic Bacterial Vaginosis.

Note: For the purposes of this indication Bacterial Vaginosis is usually defined by positive results to at least three of the four following criteria:

1. Vaginal discharge with pH > 4.5,
2. Vaginal discharge demonstrating an amine ("fishy") odour with the addition of 10% potassium hydroxide,
3. Vaginal discharge with "clue cells" on microscopy, and
4. A gram stain consistent with a diagnosis of Bacterial Vaginosis (*Lactobacillus* morphotype absent or markedly decreased; *Gardnerella* morphotype predominant flora; white blood cells absent or few; *Mobiluncus* morphotype may or may not be present).

Other pathogens which may be associated with genital infection such as *Trichomonas vaginalis*, *Candida albicans*, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* should be ruled out by appropriate laboratory means.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of DALACIN V Cream 2% is one applicator-full (approximately 5 grams) of cream intravaginally at bedtime for seven (7) consecutive days.

4.3 CONTRAINDICATIONS

Clindamycin phosphate cream is contraindicated in patients with a history of hypersensitivity to clindamycin, lincomycin or other components of the cream (see section 6.1, List of Excipients). Clindamycin phosphate cream is also contraindicated in individuals with a history of inflammatory bowel disease or history of antibiotic-associated colitis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics, including clindamycin. A toxin produced by Clostridium difficile appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with the use of antibiotics, including vaginally administered clindamycin (approximately 4% of the administered dose is absorbed systemically; see section 5.2, Pharmacokinetic Properties). Symptoms may occur up to several weeks after cessation of antibiotic therapy.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone, however in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis (eg. opiates and diphenoxylate with atropine [Lomotil]) may prolong and/or worsen the condition and should not be used.

DALACIN V Cream 2% should be used with caution in patients with a history of regional enteritis, ulcerative colitis or antibiotic associated colitis.

The use of intravaginal clindamycin phosphate may result in the localised overgrowth of non-susceptible organisms, particularly yeasts. Clindamycin has shown *in vitro* activity against Lactobacilli species which are the predominant bacteria in normal vaginal flora. In clinical trials approximately 14% of patients treated with DALACIN V Cream 2% developed symptomatic cervicitis/vaginitis predominantly due to *C. albicans* (see section 4.8, Adverse Effects (Undesirable Effects)).

The persistence of symptoms following treatment with DALACIN V Cream 2% should alert the clinician to the possibility of concomitant infection with organisms such as *Trichomonas vaginalis*, *Candida albicans*, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Appropriate microbiological investigations and therapy directed at such organisms should be considered.

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.

This cream contains mineral oil. As mineral oil may weaken latex or rubber products such as condoms or vaginal contraceptive diaphragms the use of these contraceptive devices is not recommended within 72 hours following treatment with DALACIN V Cream 2%.

DALACIN V Cream 2% contains ingredients that will cause burning and irritation of the eyes. In the event of accidental contact with the eyes, rinse the eye with copious quantities of cool tap water.

Use in the Elderly

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.

Paediatric Use

The safety and effectiveness of DALACIN V Cream 2% has not been established in children.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Cross resistance has been demonstrated between clindamycin, erythromycin and lincomycin.

No systemic drug interactions are known or anticipated with DALACIN V Cream. Antagonism has been demonstrated between clindamycin and erythromycin *in vitro* however this potential interaction would not appear to be applicable unless erythromycin was also applied intravaginally.

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.

As the studies involving DALACIN V Cream did not allow concurrent intravaginal medication to be administered there are no data regarding the concomitant use of other intravaginal medications.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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

Use in Pregnancy

CATEGORY A where the fetal membranes are intact.

Studies of DALACIN V Cream 2% have not been conducted in women during the first trimester.

Use in Lactation

It is not known if clindamycin is excreted in human breast milk following the use of vaginally administered clindamycin phosphate. Clindamycin has been reported to appear in human breast

milk in ranges from <0.5 to 3.8 micrograms/mL following systemic use. 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. Therefore, clindamycin is not recommended for nursing mothers.

If oral or intravenous 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.

4.7 EFFECT 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Non-pregnant women

In clinical trials involving non-pregnant women, medical events judged to be related, probably related, possibly related or of unknown relationship to DALACIN V Cream 2% were reported in 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 3-day or 7-day DALACIN V Cream 2% are shown in Table 1.

Table 1. Events Occurring in ⩾1% of Non-Pregnant Patients Receiving DALACIN V Cream 2%

SOC **MedDRA PT**	**DALACIN V Cream 2%**	
	3-Day	**7-Day**
	(N = 600)	**(N = 1325)**
Infections and infestations		
Vulvovaginal candidiasis	7.7%	10.4%
Vulvovaginitis	6.0%	4.4%
Vulvovaginitis trichomonal	0	1.3%
Candida infection	1.3%	0.2%
Reproductive system and breast disorders		
Vulvovaginal disorder	3.2%	5.3%

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; PT = Preferred Term; SOC = System Organ Class.

The following ADRs were reported in <1% (uncommon) of the patients receiving clindamycin vaginal cream application during clinical trials.

Infections and infestations: fungal infection, bacterial infection, skin candida, urinary tract infection, vaginal infection

Immune system disorders: hypersensitivity

Endocrine disorders: hyperthyroidism

Nervous system disorders: headache, dizziness

Ear and labyrinth disorders: vertigo

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: abdominal pain, constipation, diarrhoea, nausea, vomiting, breath odour, dyspepsia, flatulence, gastrointestinal disorder

Skin and subcutaneous tissue disorders: pruritus (non-application site), rash, rash maculopapular, urticaria, erythema

Reproductive system and breast disorders: menstrual disorder, metrorrhagia, vaginal discharge, vulvovaginal pain, endometriosis

General disorder and administration site conditions: inflammation

Investigations: microbiology test abnormal

Special senses: taste perversion

Pregnant women:

In clinical trials involving women during the second trimester of pregnancy, medical events judged to be related, probably related, possibly related or of unknown relationship to DALACIN V Cream 2% were reported in 22.8% of pregnant patients. Events occurring in ≥ 1% of patients receiving DALACIN V Cream 2% or placebo are shown in Table 2.

Table 2. Events Occurring in ⩾1% of Pregnant Patients Receiving DALACIN V Cream 2% or Placebo

SOC **MedDRA PT**	**7-Day** **N = 180**	**7-Day (Placebo)** **N = 184**
Infections and infestations		
Vulvovaginal candidiasis	13.3%	7.1%
Fungal infection	1.7%	0
Reproductive system and breast disorders		
Vulvovaginal disorder	6.7%	7.1%
Skin and subcutaneous tissue disorders		
Pruritus (non-application site)	1.1%	0
Pregnancy, puerperium and perinatal conditions		
Abnormal labour	1.1%	0.5%

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; PT = Preferred Term; SOC = System Organ Class.

Events occurring in <1% of the patients receiving DALACIN V Cream 2% with a frequency of "Uncommon" include:

Infections and infestations: candida infection, upper respiratory tract infection, vulvovaginitis trichomonal

Gastrointestinal disorders: diarrhoea

Skin and subcutaneous tissue disorders: erythema

Renal and urinary disorders: glycosuria, proteinuria, dysuria

Reproductive system and breast disorders: metrorrhagia, vulvovaginal pain

Post-Marketing Experience

Post-marketing experience of the patients receiving DALACIN V Cream 2% with a frequency category of "Frequency not known" include:

Gastrointestinal disorders: pseudomembranous colitis, abdominal distension

Musculoskeletal and connective tissue disorders: back pain

Reproductive system and breast disorders: pelvic pain

General disorder and administration site conditions: pain

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Clindamycin from DALACIN V Cream 2% may be absorbed in sufficient amounts to produce systemic effects. Acute ingestion of clindamycin has not been associated with significant toxicity. Gastrointestinal decontamination is probably not necessary in most cases.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

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.

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.

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.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis and to guide treatment. 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. 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 localised, antibiotic treatment.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Following a once a day (for seven days) dosing of approximately 5 grams of DALACIN V Cream, containing the equivalent of 100 mg clindamycin, peak serum clindamycin levels averaged 20 ng/mL (range 3 to 93 ng/mL) in normal volunteers. Approximately 3% (range 0.1 to 11.3%) of the administered dose was absorbed systemically.

In women with bacterial vaginosis, being treated with DALACIN V Cream once daily (5 grams) for seven days, the amount of clindamycin absorbed was 4% (range 0.8 to 8.2%), which approximates results seen in normal volunteers.

The levels of clindamycin absorbed following the intravaginal administration of DALACIN V Cream reached steady state within four days of the seven day regimen.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

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

Genotoxicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sorbitan monostearate,
Polysorbate 60,
Propylene glycol,
Stearic acid,
Cetostearyl alcohol,
Cetyl esters wax,
Liquid paraffin,
Purified water,
Benzyl alcohol (Each 5 g contains 50 mg benzyl alcohol as preservative).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

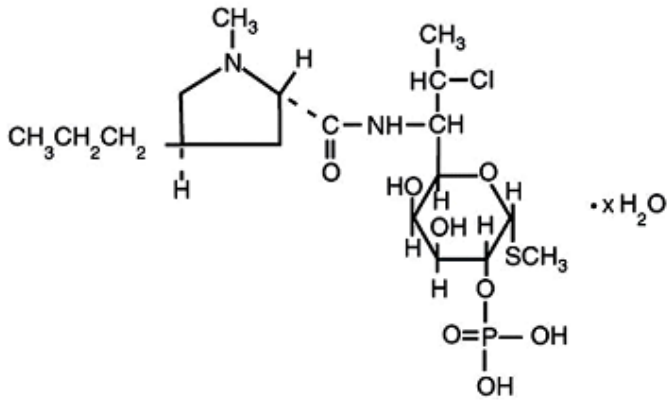
DALACIN® V Cream 2% is supplied in a 40 g collapsible laminate tube. Each 40 gram pack also contains seven (7) single-use disposable applicators, intended to be used once nightly for seven (7) days.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Clindamycin is a semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin. The MW of clindamycin phosphate is 504.96.

CAS number

CAS Registry Number: 24729-96-2.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

8 April 1994

10. DATE OF REVISION

23 April 2020

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Summary Table of Changes

Section changed	Summary of new information
4.8, 5.2, 6.1	Minor corrections/amendments to the text
8	Sponsor address updated and contact information included