# DALACIN T Topical Lotion
# (Clindamycin)

## 1. NAME OF THE MEDICINAL PRODUCT

DALACIN T

## 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.

Each mL of DALACIN T topical lotion contains clindamycin phosphate equivalent to 10 mg of clindamycin base.

## 3. PHARMACEUTICAL FORM

Topical lotion.

## 4. CLINICAL PARTICULARS

### 4.1. THERAPEUTIC INDICATIONS

DALACIN T topical lotion is indicated in the treatment of acne vulgaris.[1-8]

### 4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Route of administration: Topical (external use only).

Apply a thin film of DALACIN T topical lotion twice daily to the affected area.

DALACIN T topical lotion should be shaken immediately before using.

### 4.3. CONTRAINDICATIONS

Topical clindamycin is contraindicated in individuals with a history of hypersensitivity to clindamycin or lincomycin.

Clindamycin topical is contraindicated in individuals with a history of antibiotic-associated colitis.[12,13,14]

### 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Oral and parenteral clindamycin, as well as most other antibiotics, have been associated with severe diarrhea and pseudomembranous colitis. Use of the topical formulation of clindamycin results in

absorption of the antibiotic from the skin surface[12] (see section **5.2. Pharmacokinetic properties**). Diarrhea and colitis have been reported infrequently with topical clindamycin.[9,10]

Therefore, the physician should be alert to the possible development of antibiotic-associated diarrhea or colitis. If significant or prolonged diarrhea occurs, the drug should be discontinued and appropriate diagnostic procedures and treatment provided as necessary.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of oral and parental therapy with clindamycin.[12]

Topical clindamycin solution contains an alcohol base and can cause burning and irritation of eyes, mucous membranes and abraded skin.[1,2]

## 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.[15,16,30,31]

## 4.6. FERTILITY, PREGNANCY AND LACTATION

**Use in Pregnancy:**

Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin,[22] except at doses that caused maternal toxicity.[28] Animal reproduction studies are not always predictive of human response.

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters,[23,24,25] has not been associated with an increased frequency of congenital abnormalities.

Clindamycin 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.[28]

**Use in Nursing Mothers:**

It is not known whether clindamycin is excreted in human breast milk following use of topical clindamycin. Clindamycin has been reported to appear in human breast milk in ranges from <0.5 to 3.8 μg/mL following systemic use.[29,50,51,52]

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.[52]

## 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

| *Adverse Reactions Table*[1,31,32] | | | | | | |
|---|---|---|---|---|---|---|
| **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 | | | | | | Folliculitis* |
| Eye disorders | | | | | | Eye pain* |
| Gastrointestinal disorders | | Gastrointestinal disorder | | | | Pseudomembranous colitis*[27] Abdominal pain* |
| Skin and subcutaneous tissue disorders | Skin irritation, Dry skin, Urticaria[17] | Seborrhoea | | | | Dermatitis contact*[11] |

*: Adverse reactions identified from post-marketing experience.

## 4.9. OVERDOSE

Topically applied clindamycin can be absorbed in sufficient amounts to produce systemic effects.[12,13,14]

In the event of overdosage, general symptomatic and supportive measures are indicated as required.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis. It binds to the 50S ribosomal subunit and affects both ribosome assembly and the translation process. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin[33,34,35,36,49].

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms[37,49]:

Anaerobic gram positive non spore forming bacilli, including:

*Propionibacterium acnes.*

Pharmacodynamic effects

Efficacy is related to the time period that the agent level is above the minimum inhibitory concentration (MIC) of the pathogen (%T/MIC).[38,39,49]

Resistance

Resistance to clindamycin in *Propionibacterium acnes* can be caused by mutations at the rRNA antibiotic binding site or by methylation of specific nucleotides in the 23S RNA of the 50S ribosomal subunit. These alterations can determine cross resistance to macrolides and streptogramins B ($MLS_B$ phenotype).[40,41] Macrolide-resistant isolates should be tested for inducible resistance to clindamycin using the D-zone test.[37] Cross resistance has been demonstrated between clindamycin and lincomycin.[49]

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Particularly in severe infections or therapy failure microbiological diagnosis with verification of the pathogen and its susceptibility to clindamycin is recommended.[49]

Resistance is usually defined by susceptibility interpretive criteria (breakpoints) established by regulatory agencies, CLSI or EUCAST for systemically administered antibiotics. These breakpoints may be less relevant for topically administered clindamycin. Although clindamycin is not specifically cited, EUCAST has suggested that, for topically applied antimicrobials, resistance might be better defined by epidemiological cut-off values (ECOFFS) rather than the clinical breakpoints determined for systemic administration.[42] However, MIC distributions and ECOFFS have not been published by EUCAST for *P. acnes*. Based on correlations between clinical results in acne patients and the clindamycin MICs for their *P. acnes* isolates, values as high as 256 mg/L are considered susceptible for topically administered clindamycin.[43,49]

CLSI has published MIC ranges for a limited number (58) of unique clinical isolates of *P. acnes* collected in 2010-2012 in US hospitals; 91% of these isolates were susceptible to clindamycin (MIC $\leq$8 mg/L).[44] A recent Belgian surveillance study (2011-2012) of anaerobic bacteria included 22 *P. acnes* isolates; 95.5% were susceptible to clindamycin.[45] An earlier European surveillance study, which included 304 isolates of *P. acnes*, had reported a resistance rate of 15% to clindamycin. However, this study used a breakpoint of 0.12 mg/L; using the current breakpoint of 4 mg/L, there were no resistant isolates.[46,49]

***Breakpoints***

CLSI and EUCAST breakpoints for Gram-positive anaerobes are listed below. Although the two institutions report the values differently, the resistance breakpoint is the same, because CLSI recognized a category of intermediate susceptibility (4 mg/L). As indicated above, these breakpoints are based on use in systemic infections.[37,47,48,49]

EUCAST Breakpoints for Systemically Administered Clindamycin[47,48]

| Pathogen | Susceptible | Resistant |
|---|---|---|
| Gram-positive anaerobes (excluding *Clostridium difficile*) | ≤4 mg/L | >4 mg/L |

CLSI Breakpoints for Systemically Administered Clindamycin[37]

| Pathogen | Susceptible | Resistant |
|---|---|---|
| Anaerobes | ≤2 mg/L | ≥8 mg/L |

## 5.2. PHARMACOKINETIC PROPERTIES

Following multiple topical applications of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per mL in an isopropyl alcohol and water solution, very low levels of clindamycin are present in the serum (0–3 ng/mL) and less than 0.2% of the dose is recovered in urine as clindamycin.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of clindamycin topical solution for 4 weeks was 597 mcg/g of comedonal material (range 0-1490). Clindamycin *in vitro* inhibits all *Propionibacterium acnes* cultures tested (MICs 0.4 mcg/mL). Free fatty acids on the skin surface have been decreased from approximately 14% to 2% following application of clindamycin.[1]

**Geriatric Use**

Clinical studies for topical clindamycin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.[12]

## 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 Salmonella reversion test. Both tests were negative.[19,20]

**Impairment of Fertility:**

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m$^2$) revealed no effects on fertility or mating ability.[21]

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.[26]

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. LIST OF EXCIPIENTS

Glycerin
Methyl Paraben NF
Sodium Lauryl Sarcosuccinate
Stearic acid NF
Lexemul T
Cetostearyl Alcohol NF
Purified Water

### 6.2. INCOMPATIBILITIES

Not available

### 6.3. SHELF LIFE

24 months.

### 6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at controlled room temperature 15°C-30°C.

### 6.5. NATURE AND CONTENTS OF CONTAINER

DALACIN T topical lotion contains clindamycin phosphate equivalent to 10 mg clindamycin per gram, is available in dispensing bottle containing 30 mL of lotion.

**Dalacin T/LPD/PK-07**
**According to CDS V 11 dated: March 14, 2019; Supersedes CDS V 10 dated: June 13, 2018**

**Marketed by:**
Pfizer Pakistan Limited

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

## 7. REFERENCES

1. New Antibiotic Application for CLEOCIN Topical Solution.

2. Becker LE, *et al*; Topical clindamycin therapy for acne vulgaris. Arch Dermatol 117: 482-485, August 1981.

3. Stoughton RB, *et al*; Double-blind comparison of topical one percent clindamycin phosphate (CLEOCIN T) and oral tetracycline 500 mg/day in the treatment of acne vulgaris. Cutis 26: 424-429, October 1980.

4. Padilla RS, *et al*; Topical tetracycline hydrochloride vs. topical clindamycin phosphate in the treatment of acne. Int J Dermatol 20:445-448, 1981.

5. Gratton D, *et al*; Topical clindamycin vs systemic tetracycline in the treatment of acne. J Amer Acad Dermatol 7(1):50-53, July 1982.

6. Petersen MJ, *et al*; Evaluation of 1% clindamycin phosphate lotion in the treatment of acne: comparison with 1% clindamycin phosphate solution and lotion placebo. Curr Therap Res 49(1):232-238, July 1986.

7. Kuhlman DS and Callen JP; A comparison of clindamycin phosphate 1 percent topical lotion and placebo in the treatment of acne vulgaris. Cutis 38(3):203-206, September 1986.

8. Goltz RW, *et al*; A comparison of CLEOCIN T 1 percent solution and CLEOCIN T 1 percent lotion in the treatment of acne vulgaris. Cutis 36(3):265-268, September 1985.

9. Milstone, EB, *et al*; Pseudomembranous colitis after topical application of clindamycin. Arch Dermatol 117:154-155, March 1981.

10. Parry MF, Rha CK; Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 122:583-584, 1986.

11. Coskey RJ; Contact dermatitis due to clindamycin (Letter to the Editor). Arch Dermatol 114:446, March 1978.

12. Cleocin T United States Package Insert, November 2005.

13. Akhavan A, Bershad S; Topical Acne Drugs. Review of Clinical Properties, Systemic Exposure, and Safety. Am J Clin Dermatol 2003; 4(7): 473-492.

14. Krautheim A, Gollnick H; Transdermal Penetration of Topical Drugs Used in the Treatment of Acne. Clin Pharmacokinet 2003; 42(14): 1287-1304.

15. Fogdall RP and Miller RD; Prolongation of a Pancuronium-Induced Neuromuscular Blockade by Clindamycin. Anesthesiology 41:407-408, 1974.

16. Avery D and Finn R; Succinylcholine-Prolonged Apnea Associated with Clindamycin and Abnormal Liver Function Tests. Dis. New. Sys. 38:473-475, 1977.

17. Worldwide Labeling Safety Report: Urticaria Reported with Clindamycin, 23 Nov 05.

18. Reference no longer applicable: removed in CDS version 8.0.

19. Mazurek JH, Swenson DH. Evaluation of U-28508E in the Salmonella/microsome (Ames assay). Upjohn Technical Report 7263-81-7263-023, 01 July 1981.

20. Swenson DH. Micronucleus test in the rat. Upjohn Technical Report 0013-81-7263-001, 23 September 1981.

21. Bollart JA, Highstrete JD, Purmalis B. U-28508E: One generation rat reproduction study. Upjohn Technical Report 5401-71-7263-014, 28 June 1971.

22. Clinical Overview to support Clindamycin Topical CDS; May 2011.

23. Kass EH, *et al*. Genital mycoplasmas as a cause of excess premature delivery: Transaction of American Physicians Ninety-Fourth Seminar, 1981; 94:261-266.

24. McCormack WM, *et al*. Effect on birth weight of erythromycin treatment of pregnant women; Obstet Gynecol, 1987; 9(2):202-207.

25. Gerard GC, *et al*. Comparative efficacy of clindamycin, erythromycin, and placebo in the antenatal treatment of chlamydial infection; Upjohn Technical Report 9156-90-002, 16 February 1990.

26. 2.4 Non-Clinical Overview for Clindamycin: Embryo-fetal developmental studies in animals, November 2009.

27. 2.5 Clinical Overview Clindamycin Topical Solution, Lotion, And Gel Justification For Addition Of Pseudomembranous Colitis To Section 4.8 Of The Label May 2013.

28. Clindamycin all formulations 2013 CO for CDS update relating to use in pregnancy.

29. Steen B, Rane A. Clindamycin passage into human milk; Br J Clin Pharmacol, 1982; 13:661-664.

30. Sloan PA, Rasul M. Prolongation of rapacuronium neuromuscular blockade by clindamycin and magnesium. Anesth Analg 2002;94:123-4.

31. June 2014_Clindamycin phosphate_2.5 Clinical Overview to Assign the Frequency Category to Adverse Drug Reactions in Section 4.8 of the CDS.

32. Report of CIOMS Working Groups III and IV, Guidelines for Preparing Core Clinical-Safety Information on Drugs, Second Edition.

33. Nord CE, Oprica C. Antibiotic resistance in Propionibacterium acnes. Microbiological and clinical aspects. Anaerobe. 2006; 12:207-10.

34. Spazek H, Rezanka T. Lincomycin, clindamycin, and their applications. Appl Microbiol Biotechnol 2004;64:455-64.

35. Champney WS, Tober CL. Specific inhibition of 50S ribosomal subunit formation in *Staphylococcus aureus* cells by 16-membered macrolide, lincosamide, and streptogramin B antibiotics. Curr Microbiol 2000; 41: 126-35.

36. Amr S, Brown MB, Martin GP *et al*. Activation of clindamycin phosphate by human skin. J Appl Microbiol 2001; 90: 550-4.

37. Clinical and Laboratory Standards Institute (CLSI). 2017. *Performance Standards for Antimicrobial Susceptibility Testing*. 27th ed. CLSI Supplement M100. CLSI, Wayne, Pennsylvania, 2017.

38. Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. Clin Infect Dis 2004;864-70.

39. Craig WA. Does the dose matter? Clin Infect Dis 2001;33 (Suppl 3):S233-7.

40. Rosato A, Vicarini H, Leclercq R. Inducible or constitutive expression of resistance in clinical isolates of streptococci and enterococci cross-resistant to erythromycin and lincomycin. J Antimicrob Chemother 1999;43:559-62.

41. Weisblum B. Erythromycin resistance by ribosome modification. Antimicrob Agents Chemother 1995;39:577-85.

42. EUCAST. EUCAST ECOFFS for topical agents. 26 March 2012.

43. Leyden JJ. 2012. *In vivo* antibacterial effects of tretinoin-clindamycin and clindamycin alone on Propionibacterium acnes with varying clindamycin minimum inhibitory. J Drugs Dermatol. 11(12):1434-8.

44. Clinical and Laboratory Standards Institute (CLSI). 2016. Performance Standards for Antimicrobial Susceptibility Testing; 26th ed. CLSI Supplement M100S. Appendix D. CLSI. Wayne, Pennsylvania, 2016.

45. Wybo I, Van den Bossche D, Soetens O. Fourth Belgian multicentre survey of antibiotic susceptibility of anaerobic bacteria. J Antimicrob Chemother. 2014;69(1):155-61.

46. Oprica C, *et al*. European surveillance study on the antibiotic susceptibility of Propionibacterium acnes. Clin Microbiol Infect. 2005;11(5):204-13.

47. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0, 2017.

48. European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. In: European Committee on Antimicrobial Susceptibility Testing (EUCAST). Version 7.0;2017:1-17.

49. 2.5 Clinical Overview, Updates to Section 5.1 Pharmacodynamic Properties of the Core Data Sheet, December 2017.

50. Matsuda S, Mori S, Azuma S. Clinical evaluation of clindamycin in gyneco-obstetrics. Chemotherapy (Tokyo) 1969;17:899-900.

51. Smith JA, Morgan JR, Rachlis AR, et al. Clindamycin in human breast milk. Can Med Assoc J 1975;112:806.

52. 2.5 Clinical Overview to support updates to section 4.6 Fertility, Pregnancy and Lactation of the Core Data Sheet, May 2018.