AUSTRALIAN PRODUCT INFORMATION - DALACIN® T (Clindamycin phosphate) 1% Topical Lotion

1. NAME OF THE MEDICINE

Clindamycin phosphate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DALACIN T lotion contains clindamycin phosphate equivalent to clindamycin 10 mg/mL, in an aqueous base.

Excipient of known effect:

- Methyl hydroxybenzoates

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

3. PHARMACEUTICAL FORM

Lotion.

White to off-white emulsion.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DALACIN T topical lotion is indicated in the treatment of acne vulgaris, particularly forms in which comedones, papules and pustules predominate.

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

The efficacy of DALACIN T lotion has not been demonstrated beyond 12 week's duration. Please refer to section 5.1, Pharmacodynamic Properties, Clinical Trials.

4.3 CONTRAINDICATIONS

DALACIN T topical lotion is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

DALACIN T topical lotion is also contraindicated in individuals with a history of inflammatory bowel disease or a history of antibiotic-associated colitis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Oral and parenteral clindamycin have been associated with severe diarrhoea and pseudomembraneous colitis which may result in patient death. Use of the clindamycin phosphate topical lotion (DALACIN T) results in absorption of the antibiotic from the skin surface. Diarrhoea, bloody diarrhoea and pseudomembraneous colitis have been reported with the use of topical and systemic clindamycin.

It is important to consider the diagnosis of antibiotic-associated colitis in patients who develop diarrhoea or colitis associated with antibiotic use. Antibiotic-associated colitis (whether pseudomembraneous or not) appears to result from a toxin produced by *Clostridium difficile* in the alimentary tract. The severity of the colitis may range from mild watery diarrhoea to severe, persistent, life-threatening bloody diarrhoea. The diagnosis is usually made by recognition of the clinical symptoms. The symptoms may occur during therapy or up to several weeks after cessation of therapy. Additional confirmatory signs of antibiotic-associated colitis include pseudomembrane formation seen with colonoscopy, *C. difficile* culture from the stool, or assay of the stool for *C. difficile* toxin.

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

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (LOMOTIL®), may prolong and/or worsen the condition and should not be used.

DALACIN T should be prescribed with caution in atopic individuals.

For external use only. Avoid contact with sensitive surfaces such as the eyes, lips and mucous membranes.

DALACIN T is not generally effective in severe (nodulocystic) acne.

Use of topical clindamycin (DALACIN T) has been associated with the development of strains of *Propioniibacterium acnes* resistant to clindamycin in some patients. If there is evidence of the development of clinical resistence during treatment, consideration should be given to discontinuation of treatment with topical antibiotics.

Use in the elderly

Clinical studies for DALACIN T did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Antagonism has been demonstrated in between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, these two drugs should not be administered concurrently.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility was not impaired in rats given 300 mg/kg/day in the diet.

Use in pregnancy

Category A

Reproductive studies have been performed in rats and mice using oral and parenteral doses of clindamycin phosphate up to 300 mg/kg/day and have revealed no evidence of harm to the fetus due to clindamycin. There are however, no adequate and well-controlled studies in pregnant women.

Use in lactation

It is not known if clindamycin is excreted in human breast milk following the use of topically 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 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The tables below list the adverse effects identified through clinical study experience and post-marketing surveillance. The most common adverse reactions are abdominal pain, gastrointestinal disorders, skin irritation, urticaria, dry skin and seborrhoea.

Clinical trial data

Table 1. Adverse events reported with DALACIN T topical lotion, solution and placebo in 5 USA comparative clinical studies. Included are all adverse events with an incidence ≥ 1% in any treatment group.[1]

	Number of patients that experienced an adverse event					
	Lotion		Solution		Placebo	
System organ class	(N=121)		(N=52)		(N=103)	
	n	**%**	**n**	**%**	**n**	**%**
Total number of patients with adverse events	29	24.0	16	30.8	31	30.1
General disorders and administration site conditions						
Cold/flu	6	5.0	-	-	3	2.9
Dental procedure	1	0.8	1	1.9	-	-
Renal and urinary tract disorders						
Urinary tract infection	3	2.5	-	-	1	1.0
Gastrointestinal disorders						
Diarrhoea	5	4.1	5	9.6	5	4.9
Vomiting	1	0.8	1	1.9	1	1.0
Abdominal cramps, pain	-	-	3	5.8	1	1.0
Nausea	-	-	1	1.9	2	1.9
Reproductive system and breast disorders						
Vaginitis	-	-	1	1.9	-	-
Respiratory, thoracic and mediastinal disorders						
Sore throat/tonsillitis/ Laryngitis	3	2.5	-	-	5	4.9
Upper respiratory tract infection/cough/tracheitis	1	0.8	-	-	3	2.9
Sinusitis/congestion	-	-	2	3.8	-	-
Psychiatric disorders						
Anxiety	-	-	-	-	2	1.9
Musculo-skeletal and connective tissue disorders						
Fracture	1	0.8	2	3.8	-	-
Skin and subcutaneous tissue disorders						
Skin problems	3	2.5	1	1.9	1	1.0

1. Note that a causal relationship to the study treatment has not been determined.

Post-marketing experience

Table 2. The following adverse events have been reported since marketing of DALACIN T lotion in spontaneous post-marketing surveillance:[1,2]

Immune system disorders	
Rare	Allergic reaction.
General disorders and administration site conditions	
Very rare	Oedema.
Cardiovascular system	
Very rare	Rapid heartbeat, chest tightness.
Gastrointestinal disorders	

Common *Rare* *Very rare*	Diarrhoea, nausea. Abdominal pain. Acute colitis, bloating, constipation, coloured tongue, dyspepsia, flatulence, gastrointestinal distress, gastrointestinal reflux, heartburn, pseudomembraneous colitis, rectal bleeding, vomiting.
Metabolism and nutrition disorders	
Very rare	Weight loss.
Blood and lymphatic system disorders	
Very rare	Leukopenia.
Nervous system disorders	
Very rare	Headache, dizziness, facial numbness, metallic taste, voice loss.
Reproductive system and breast disorders	
Very rare	Fertility disorders.
Respiratory, thoracic and mediastinal disorders	
Very rare	Epistaxis, sore throat.
Skin and subcutaneous tissue disorders	
Very common *Common* *Uncommon* *Rare* *Very rare*	Skin irritation, dry skin, urticaria. Seborrhoea. Burning sensation, rash, erythema. Pruritis, contact dermatitis, facial swelling. Blisters, hair loss, papular pruritic skin rash, skin inflammation, scaling, skin discolouration.
Eye disorders	
Very rare	Eye irritation.
Frequency not known	Eye pain.
Infections and infestations	
Very rare	Fungal infection, bladder infection, folliculitis.
Investigations	
Very rare	Elevated liver enzymes.

1. Note that a causal relationship to DALACIN T topical lotion has not been determined.
2. Frequencies estimated from spontaneous reporting.
   Very Common (≥ 10%), Common (≥1% and <10%), Uncommon (≥0.1% and <1%), Rare (≥0.01% and <0.1%) and Very Rare (<0.01%), Frequency not known (cannot be estimated from available data).

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

Topically applied DALACIN T can be absorbed in sufficient amounts to produce systemic effects. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

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. 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.

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

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).

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). Macrolide-resistant isolates should be tested for inducible resistance to clindamycin using the D-zone test. Cross resistance has been demonstrated between clindamycin and lincomycin.

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.

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. 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.

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 ≤8 mg/L). A recent Belgian surveillance study (2011-2012) of anaerobic bacteria

included 22 *P. acnes* isolates; 95.5% were susceptible to clindamycin. 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.

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.

EUCAST Breakpoints for Systemically Administered Clindamycin

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

CLSI Breakpoints for Systemically Administered Clindamycin

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

Clinical trials

Five randomised, controlled clinical trials have been performed to evaluate the efficacy and safety of clindamycin phosphate topical lotion in patients with moderate to severe acne vulgaris (defined in the studies as 12 to 70 inflammatory pustules and no more than 6 cystic lesions on the face). All studies were either double-blind or investigator blind studies. Four studies compared the lotion with placebo and two of these studies also included clindamycin phosphate solution (an alcohol based formulation) as a comparator. Efficacy was based upon the reduction in numbers of acne lesions (including papules, pustules and open and closed comedones).

A total of 362 patients were enrolled in these comparative studies, and 276 patients were evaluable for efficacy. Patients were evaluated at 3, 6, 9 and 12 weeks.

A statistically significant change ($p<0.05$) in mean acne lesion scores from baseline favouring DALACIN T lotion (n = 47) over placebo (n = 48) was seen in one study. There was a trend for DALACIN T (n = 56) to produce a superior response to placebo (n = 55) in three other studies in the observation period. The adverse events recorded during treatment with the lotion in these studies were minor and unrelated to therapy.

5.2 PHARMACOKINETIC PROPERTIES

Following multiple topical applications of clindamycin phosphate lotion 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 serum (Cmax 2.7 ng/mL) and about 0.23% of the dose is recovered in urine as clindamycin.

Clindamycin in the serum is extensively metabolised. Approximately 10% of an oral dose is excreted as biologically active clindamycin in urine. Inactive metabolites are also excreted in urine.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of clindamycin phosphate topical solution for 4 weeks was 597 μg eq/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 a 1% clindamycin solution containing alcohol.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

Long-term studies in animals to evaluate the carcinogenic potential of clindamycin phosphate have not been performed.

Genotoxicity

Clindamycin phosphate was negative in assays evaluating the potential to cause gene mutations and chromosomal damage.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Glycerol,
Sodium lauroyl sarcosinate,
Stearic acid,
Glyceryl monostearate,
Mono- and di- glycerides,
Purified water,
Potassium hydroxide,
Cetostearyl alcohol,
Isostearyl alcohol,
Methyl hydroxybenzoate.

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 25 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

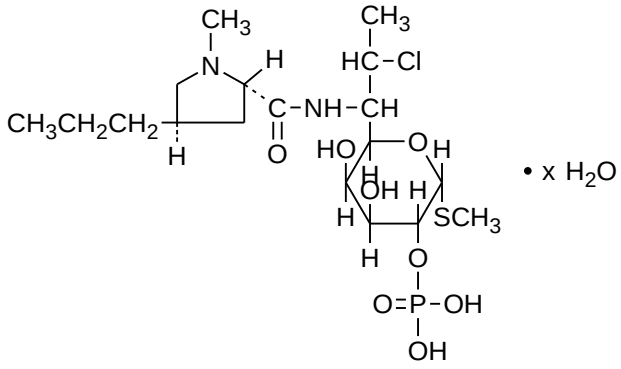
DALACIN T topical lotion is available in 60 mL bottles.

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



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-2-0-dihydrogen phosphate. It has a molecular weight of 504.96, and the molecular formula is $C_{18}H_{34}C1N_20_8PS$.

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. It is a white to off-white, odourless, hygroscopic, crystalline powder, found to be soluble in water, slightly soluble in dehydrated alcohol, sparingly soluble in dehydrated alcohol, sparingly soluble in acetone, and practically insoluble in chloroform and ether.

CAS number

CAS Registry Number: 24729-96-2.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (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

22 February 1999

10. DATE OF REVISION

23 April 2020

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Summary Table of Changes

Section changed	Summary of new information
6.1	Minor amendment to text
8	Sponsor address updated and contact information included