DALACIN T®

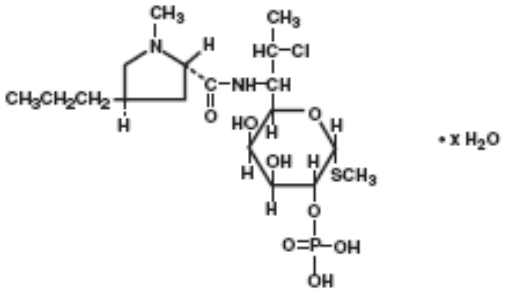
PHARMACEUTICAL FORM
Topical Solution and Topical Lotion.

For External Use
DESCRIPTION
Each mL of DALACIN T Topical Solution contains clindamycin phosphate equivalent to 10 mg of clindamycin base.

Each mL of DALACIN T Topical Lotion contains clindamycin phosphate equivalent to 10 mg of clindamycin base.

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 structural formula is represented below:



Molecular formula: $C_{18}H_{34}ClN_2O_8PS$

The chemical name for clindamycin phosphate is 7(S)-chloro-7-deoxylincomycin-2-phosphate (MW=504.96).

DALACIN T Topical Solution is supplied in bottles containing 30 mL of topical solution. In addition to clindamycin phosphate, the topical solution contains propylene glycol, isopropyl alcohol 0.5 mL, and purified water.

DALACIN T Topical Lotion is supplied in bottles containing either 30 mL or 60 mL of lotion. In addition to clindamycin phosphate, the topical lotion contains sodium lauroyl sarcosinate, methylparahydroxybenzoate, glycerol, stearic acid, lexemul T, cetostearyl alcohol, isostearyl alcohol, and purified water.

PHARMACOLOGICAL PROPERTIES
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

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.

Following multiple topical application of clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per gram in the gel formulation, 0.053% (morning) and 0.070% (evening) of the administered dose was recovered in the urine as clindamycin. Average absolute bioavailability was 1.6% and 2.2% after morning and evening doses, respectively.

Clindamycin activity has been demonstrated in comedones from acne patients. The mean concentration of antibiotic activity in extracted comedones after application of clindamycin (10 mg/mL) in an isopropyl alcohol and water solution for 4 weeks was 597 mcg/g of comedonal material (range 0-1490 mcg/g). 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.

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.

INDICATIONS

DALACIN T Topical Solution and Lotion are indicated in the treatment of acne vulgaris.

PRECAUTIONARY STATEMENTS

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 (see Pharmacokinetic properties). Diarrhea and colitis have been reported infrequently with topical clindamycin. 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. Large bowel endoscopy should be considered in cases of severe diarrhea. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition.

DALACIN T Topical Solution contains an alcohol base and can cause burning and irritation of eyes, mucous membranes and abraded skin. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes) bathe with copious amounts of cool water.

The solution has an unpleasant taste and caution should be exercised when applying the medication around the mouth.

Prolonged use of DALACIN T Topical Solution for several months must be under the control of a physician.

CONTRAINDICATIONS

DALACIN T is contraindicated in individuals with a history of hypersensitivity to clindamycin or lincomycin, or a history of antibiotic-associated colitis.

ADVERSE REACTIONS

Adverse Reactions Table						
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* Abdominal pain*
Skin and subcutaneous tissue disorders	Skin irritation, Dry skin, Urticaria	Seborrhoea				Dermatitis contact*

*: Adverse reactions identified from post-marketing experience.

Recommendations on Use in Pregnancy and by Nursing Mothers

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, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

In clinical trials with limited number of pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. However, there are no adequate and well-controlled studies using clindamycin in pregnant women during the first trimester of pregnancy and this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether clindamycin is excreted in human breast milk following use of DALACIN T. Clindamycin has been reported to appear in human breast milk in ranges from <0.5 to 3.8 mcg/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. 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.

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.

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.

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.

Interactions

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.

Effect on Ability to Drive and Use Machines

It is not expected that DALACIN T would interfere with the ability to drive or operate machinery.

Overdose

DALACIN T is intended for topical use only. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), rinse affected area with copious amounts of

cool water. Topically applied clindamycin phosphate can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONARY STATEMENTS).

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

DOSAGE AND ADMINISTRATION
Apply a thin film of DALACIN T Topical Solution or Lotion to the affected area of clean, dry skin twice daily. Massage into the skin is not needed. Contact with eyes and mouth should be avoided. Rinse hands after application.

Dalacin T Topical Lotion should be shaken immediately before using.

Storage and Stability
Do not store above 25°C. Protect from freezing.

Packaging
DALACIN T Topical Solution is packaged in a bottle with applicator of 30 mL. The medicine comes in a bottle that has a separate applicator and cap.

To use the applicator:
1) remove cap from the bottle and discard;
2) firmly press applicator into bottle;
3) seal firmly by tightening domed-cap.
The pharmacist may have assembled the bottle for you, in which case the applicator top will already be attached to the bottle.

DALACIN T Topical Lotion is packaged in bottles containing either 30 mL or 60 mL of lotion.

Product Owner
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