

In this patient, recurrent nodules and plaques of adenosquamous carcinoma are visible at the edge of a scar from previous treatment.



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# Adenosquamous Carcinoma Is Aggressive, Easily Missed

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VANCOUVER, B.C. — Adenosquamous carcinoma is an often misdiagnosed and more aggressive type of skin cancer that requires close follow-up for possible recurrences, according to a review that identified 27 patients with primary disease.

“We are starting to get the sense that it can be very clinically aggressive and, in fact, may be more aggressive than conventional cutaneous squamous cell carcinoma [SCC], with a high risk of local recurrence,” Dr. Jennifer M. Fu said at the annual meeting of the American College of Mohs Surgery.

A rise in the number of cases at her institution in recent years, with some of them proving to be very locally aggressive, prompted a closer look at this cancer. Dr. Fu and her colleagues searched their institution's records for the past 10 years to identify cases of adenosquamous carcinoma (ASC) diagnosed there. The search identified 27 patients with primary ASC, 7 of whom experienced a recurrence. The patients had a mean age of 74 years (range 50-97 years), and 70% were men.

Some 56% of the primary tumors were on the face, 15% were on the scalp, and 15% were on the arm or shoulder. “Clinically, this was a very difficult diagnosis for people to make, often presenting just as a firm papule or plaque and not infrequently ulcerated,” observed Dr. Fu, a dermatology resident at the University of California, San Francisco.

“Most of the clinicians diagnosed this as something else—as basal cell carcinoma, scar, metastatic carcinoma, rosacea in one case, and a spider bite in another case,” she said. “In no case was adenosquamous carcinoma correctly diagnosed.”

Histopathologically, many of the features of ASC overlap those of desmoplastic SCC, but ASC differs in having glandular differentiation. “At least at our institution, we feel that adenosquamous carcinoma is probably best considered a variant of SCC and on a spectrum of desmoplastic SCC,” Dr. Fu said.

The tumors evaluated in the study typically had an infiltrative pattern with dermal fibrosis or sclerosis: 61% showed elastosis, while 30% were ulcerated. Squamous differentiation was universal, with all tumors exhibiting cytoplasmic cornification and 41% having keratinizing cysts.

Most tumors (92%) had ductular elements, while 58% had glandular elements. Even when a tumor had glandular elements, the percentage of that tumor showing those elements varied from roughly 5% to 80%. In fact, two of the cases were initially interpreted to be SCC but were subsequently determined to have glandular differentiation more consistent with ASC. In such equivocal cases, immunostaining for carcinoembryonic antigen or cytokeratin 7 may help identify glandular foci, she noted.

Clinical outcomes were assessed in the six patients who received most of their treatment at her hospital. Five were immunosuppressed. All underwent Mohs surgery at least once, and two received adjuvant radiation therapy and cetuximab (Erbix) for locally advanced disease. For these patients, “the Mohs defect postoperatively far exceeded what was evident clinically,” said Dr. Fu, who had no conflicts of interest in association with the study. ■

## ClindaReach™

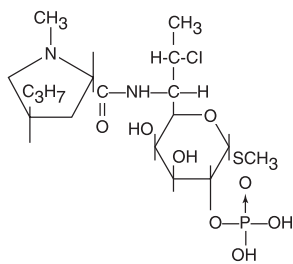
(Clindamycin Phosphate Topical Solution USP, 1%) Pledgets  
For External Use Only

### DESCRIPTION

ClindaReach™ (Clindamycin Phosphate Topical Solution USP, 1%), Pledgets (ClindaReach™) contain clindamycin phosphate, USP at a concentration equivalent to 10 mg clindamycin per milliliter. Each ClindaReach™ pledget applicator contains approximately 1 mL of topical solution.

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 solution contains isopropyl alcohol 50% v/v, propylene glycol, sodium hydroxide (to adjust the pH to between 4.0-7.0) and purified water. The structural formula is represented below:



The chemical name for clindamycin phosphate is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinedicarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2- (dihydrogen phosphate). It has a molecular weight of 504.96, and the molecular formula is C<sub>18</sub>H<sub>34</sub>ClN<sub>2</sub>O<sub>8</sub>PS. Flash point 75°F.

### CLINICAL PHARMACOLOGY

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

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

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 Phosphate 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.

### INDICATIONS AND USAGE

ClindaReach™ is indicated in the treatment of acne vulgaris. In view of the potential for diarrhea, bloody diarrhea and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS and ADVERSE REACTIONS.)

### CONTRAINDICATIONS

ClindaReach™ is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

### WARNINGS

Orally and parenterally administered clindamycin has been associated with severe colitis which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis. Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

When significant diarrhea occurs, the drug should be discontinued. Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea.

Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic-associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dosage is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

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

### PRECAUTIONS

#### General

ClindaReach™ contains an alcohol base that will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), bathe with copious amounts of cool tap water. The solution has an unpleasant taste and caution should be exercised when applying medication around the mouth.

ClindaReach™ should be prescribed with caution in atopic individuals.

#### Drug Interactions

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.

#### Pregnancy: Teratogenic Effects—Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 100 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

#### Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of ClindaReach™. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### Pediatric Use

Safety and effectiveness in pediatric patients under the age of 12 have not been established.

### ADVERSE REACTIONS

In 18 clinical studies of various formulations of topical Clindamycin Phosphate using placebo vehicle and/or active comparator drugs as controls, patients experienced a number of treatment emergent adverse dermatologic events [see table below].

Treatment Emergent Adverse Event	Number of Patients Reporting Events		
	Solution n=553 (%)	Gel n=148 (%)	Lotion n=160 (%)
Burning	62 (11)	15 (10)	17 (11)
Itching	36 (7)	15 (10)	17 (11)
Burning/Itching	60 (11)	# (—)	# (—)
Dryness	105 (19)	34 (23)	29 (18)
Erythema	86 (16)	10 (7)	22 (14)
Oiliness/Oily Skin	8 (1)	26 (18)	12* (10)
Peeling	61 (11)	# (—)	11 (7)

# not recorded

\* of 126 subjects

Orally and parenterally administered clindamycin has been associated with severe colitis which may end fatally.

Cases of diarrhea, bloody diarrhea and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and rarely with topical clindamycin (see WARNINGS).

Abdominal pain and gastrointestinal disturbances as well as gram-negative folliculitis have also been reported in association with the use of topical formulations of clindamycin.

### OVERDOSAGE

Topically applied ClindaReach™ can be absorbed in sufficient amounts to produce systemic effects. (See WARNINGS.)

### DOSAGE AND ADMINISTRATION

Apply a thin film of ClindaReach™ twice daily to affected area. More than one pledget may be used. Each pledget should be used only once and then be discarded.

Pledget: Remove pledget from jar just before use. Do not use if the seal under the cap is broken. Discard after single use.

Keep all liquid dosage forms in containers tightly closed.

### HOW SUPPLIED

ClindaReach™ Pledgets contain Clindamycin Phosphate Topical Solution. The solution contains Clindamycin Phosphate equivalent to 10 mg clindamycin per milliliter.

ClindaReach™ is supplied as 120 single use pledgets, packaged as two jars of 60 single use pledgets each.

Store at controlled room temperature 15° to 30°C (59° to 86°F) [See USP]. Protect from freezing. Flash Point 75°F.

R only

Manufactured for: Sirius Laboratories,  
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DUSA®

Manufactured by:  
PERRIGO, Bronx, NY 10457  
Patent pending

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