CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-801

APPROVED LABELING

1.3.2.1 Draft Package Insert

Prescribing Information Text

Evoclin™

(clindamycin phosphate) Foam, 1%

Rx Only

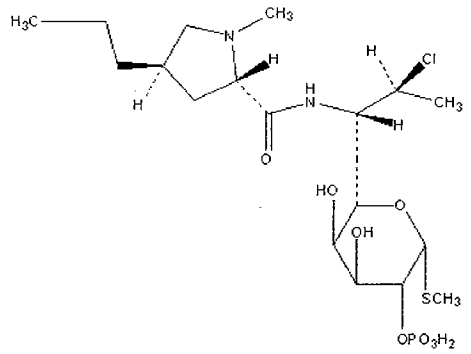
FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION

Evoclin (clindamycin phosphate) Foam, 1%, a topical antibiotic in a foam vehicle, contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram in a vehicle consisting of cetyl alcohol, dehydrated alcohol (ethanol 58%), polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl alcohol, pressurized with a hydrocarbon (propane/butane) propellant.

Chemically, 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, and has the structural formula represented below:

Figure 1: Structural Formula



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-(dihydrogen phosphate).

CLINICAL PHARMACOLOGY

Pharmacokinetics: In an open label, parallel group study in 24 patients with acne vulgaris, 12 patients (3 male and 9 female) applied 4 grams of Evoclin Foam once-daily for five days, and 12 patients (7 male and 5 female) applied 4 grams of Clindagel® (clindamycin phosphate) Topical Gel, 1%, once daily for five days. On Day 5, the mean C_{max} and AUC(0-12) were 23% and 9% lower, respectively, for Evoclin Foam than for Clindagel®.

Following multiple applications of Evoclin Foam less than 0.024% of the total dose was excreted unchanged in the urine over 12 hours on Day 5.

Microbiology: The clindamycin component has been shown to have in vitro activity against *Propionibacterium acnes*, an organism which is associated with acne vulgaris; however, the clinical significance of this activity against *P. acnes* was not examined in clinical trials with this product. Cross-resistance between clindamycin and erythromycin has been demonstrated.

CLINICAL STUDIES

In one multicenter, randomized, double-blind, vehicle-controlled clinical trial patients with mild to moderate acne vulgaris used Evoclin (clindamycin phosphate) Foam, 1% or the vehicle foam once daily for twelve weeks. Treatment response, defined as the proportion of patients clear or almost clear, based on the Investigator Static Global Assessment (ISGA), and the mean percent reductions in lesion counts at the end of treatment in this study are shown in the following table:

Efficacy Parameters	Evoclin Foam N=386	Vehicle Foam N=127
Treatment response (ISGA)	31%	18%*
Percent reduction in lesion counts		
Inflammatory Lesions	49%	35%*
Noninflammatory Lesions	38%	27%*
Total Lesions	43%	31%*

* P< 0.05

INDICATIONS AND USAGE

Evoclin is indicated for topical application 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

Evoclin 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.

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

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Avoid contact of Evoclin with eyes. If contact occurs, rinse eyes thoroughly with water.

PRECAUTIONS

General: Evoclin 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity of a 1% clindamycin phosphate gel similar to Evoclin was evaluated by daily application to mice for two years. The daily doses used in this study were approximately 3 and 15 times higher than the human dose of clindamycin phosphate from 5 milliliters of Evoclin, assuming complete absorption and based on a body surface area comparison. No significant increase in tumors was noted in the treated animals.

A 1% clindamycin phosphate gel similar to Evoclin caused a statistically significant shortening of the median time to tumor onset in a study in hairless mice in which tumors were induced by exposure to simulated sunlight.

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

Reproduction studies in rats using oral doses of clindamycin hydrochloride and clindamycin palmitate hydrochloride have revealed no evidence of impaired fertility.

Pregnancy: Teratogenic effects - Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin phosphate, clindamycin hydrochloride and clindamycin palmitate hydrochloride. These studies revealed no evidence of fetal harm. The highest dose used in the rat and mouse teratogenicity studies was equivalent to a clindamycin phosphate dose of 432 mg/kg. For a rat, this dose is 84 fold higher, and for a mouse 42 fold higher, than the anticipated human dose of clindamycin phosphate from Evoclin based on a mg/m^2 comparison. 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 Evoclin. 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 of Evoclin in children under the age of 12 have not been studied.

Geriatric Use: The clinical study with Evoclin did not include sufficient numbers of patients aged 65 and over to determine if they respond differently than younger patients.

ADVERSE REACTIONS

The incidence of adverse events occurring in ≥1% of the patients in clinical studies comparing Evoclin and its vehicle is presented below:

Selected Adverse Events Occurring in ≥1% of Subjects

Adverse Event	Number (%) of Subjects	
	Evoclin Foam N=439	Vehicle Foam N=154
Headache	12 (3%)	1 (1%)
Application site burning	27 (6%)	14 (9%)
Application site pruritus	5 (1%)	5 (3%)
Application site dryness	4 (1%)	5 (3%)
Application site reaction, not otherwise specified	3 (1%)	4 (3%)

In a contact sensitization study, none of the 203 subjects developed evidence of allergic contact sensitization to Evoclin.

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

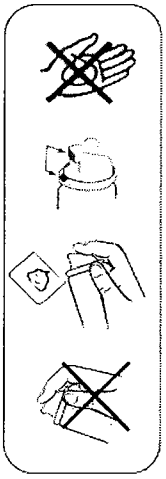
Topically applied Evoclin may be absorbed in sufficient amounts to produce systemic effects (see WARNINGS).

DOSAGE AND ADMINISTRATION

Apply Evoclin once daily to affected areas after the skin is washed with mild soap and allowed to fully dry. Use enough to cover the entire affected area.

To Use Evoclin:

1. Do not dispense Evoclin directly onto your hands or face, because the foam will begin to melt on contact with warm skin.
2. Remove the clear cap. Align the black mark with the nozzle of the actuator.
3. Hold the can at an upright angle and then press firmly to dispense. Dispense an amount directly into the cap or onto a cool surface. Dispense an amount of Evoclin that will cover the affected area(s). If the can seems warm or the foam seems runny, run the can under cold water.



4. Pick up small amounts of Evoclin with your fingertips and gently massage into the affected areas until the foam disappears.

Throw away any of the unused medicine that you dispensed out of the can.

Avoid contact of Evoclin with eyes. If contact occurs, rinse eyes thoroughly with water.

HOW SUPPLIED

Evoclin containing clindamycin phosphate equivalent to 10 mg clindamycin per gram, is available in the following size: 50 gram can - NDC 63032-061-50

STORAGE AND HANDLING

Store at controlled room temperature 20°-25°C (68° - 77°F).

FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.

Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperature above 120°F (49°C).

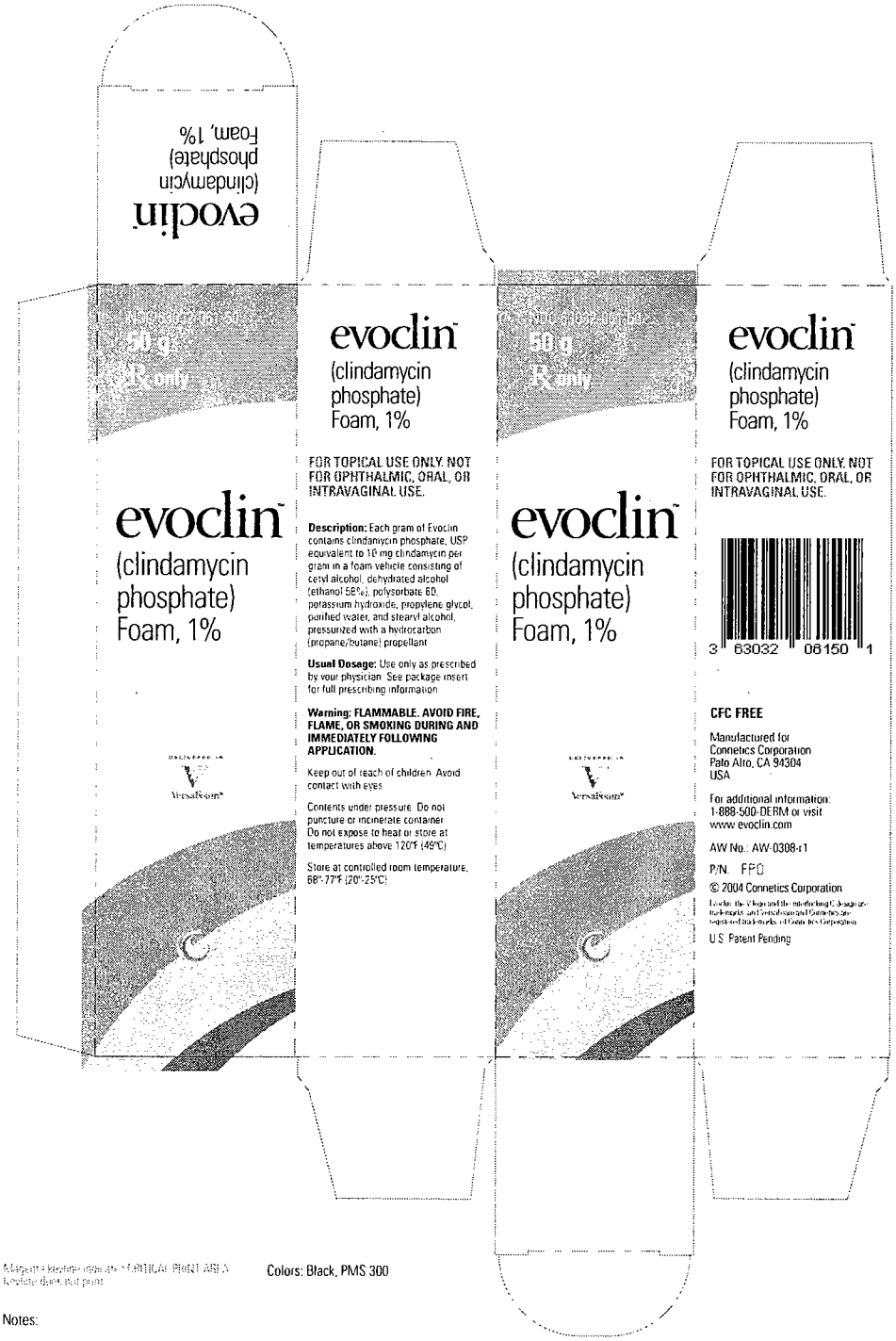
Keep out of reach of children.

Manufactured for
Connetics Corporation
Palo Alto, CA 94304
USA

For additional information:
1-888-500-DERM or visit
www.evoclin.com

U.S. Patent Pending

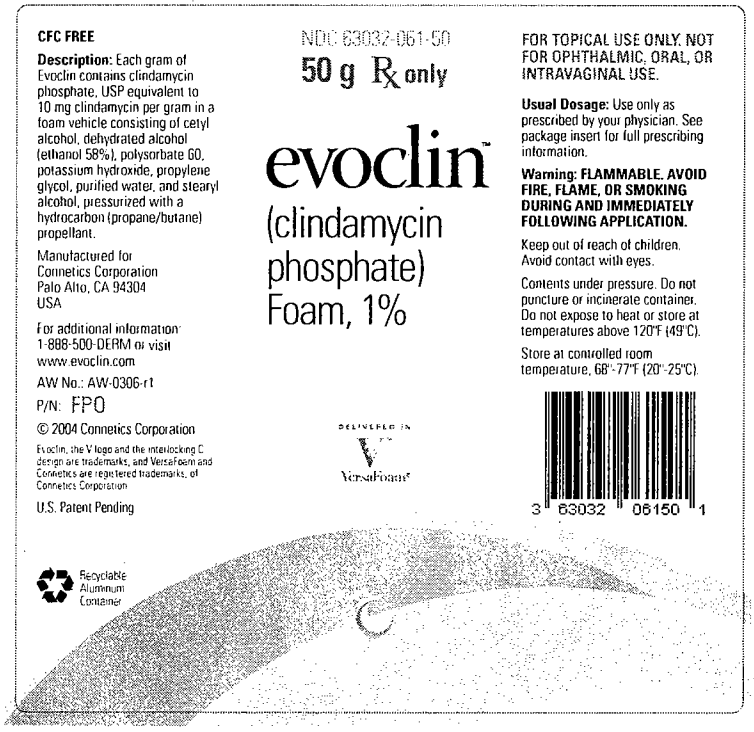
connetics®



Colors: Black, PMS 300

Notes:

1. Manufacturer must strip in a part number in the area designated FPO.
2. Manufacturer must submit 3 copies of the proof to Connetics Pkg Eng and Operations prior to production of new/revised parts.



Magenta Keyline indicates CRITICAL PRINT AREA
Keyline does not print

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/s/

Stanka Kukich
10/22/04 02:43:21 PM
Sign off for Dr. Jonathan Wilkin, Division Director