PDR®

66

EDITION

2012

PHYSICIANS' DESK REFERENCE®

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Table 9. Summary of Efficacy Data*

	Study 1	Study 2	
	Zevalin therapeutic regimen N = 54	Zevalin therapeutic regimen N = 64	Rituximab N = 66
Overall Response Rate (%)	74	83	55
Complete Response Rate† (%)	15	38	18
Median DR‡,§ (Months) [Range¶]	6.4 [0.5-49.9+]	14.3 [1.8-47.6+]	11.5 [1.2-49.7+]
Median TTP‡,#(Months) [Range¶]	6.8 [1.1-50.9+]	12.1 [2.1-49.0+]	10.1 [0.7-51.3+]

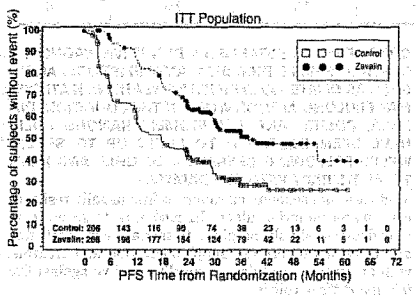
* IWRC: International Workshop Response Criteria
† CRu and CR: Unconfirmed and confirm complete response
‡ Estimated with observed range
§ Duration of response: interval from the onset of response to disease progression
¶ "+" indicates an ongoing response
# Time to Disease Progression: interval from the first infusion to disease progression

men (83% vs. 55%, p<0.001). Time-to-disease-progression was not significantly different between study arms. Table 9 summarizes efficacy data from Study 2.
[See table 9 above]
Study 3 was a single arm study of 30 patients of whom 27 had relapsed or refractory low-grade, follicular NHL and a platelet count 100,000 to 149,000/mm^3. Patients with ≥ 25% lymphomatous marrow involvement, prior myeloablative therapy with stem cell support, prior external beam radiation to > 25% of active marrow or neutrophil count <1,500/mm^3 were ineligible for Study 3. All patients received Y-90 Zevalin [0.3 mCi per kg (11.1 MBq per kg)]. Objective, durable clinical responses were observed [89% ORR (95% CI: 70-97%) with a median duration of response of 11.6 months (range: 1.0-42.4+ months)].

14.2 Follicular, B-Cell NHL Upon Completion of First-Line Chemotherapy

Study 4 was a multi-center, randomized, open-label study conducted in patients with follicular NHL with a partial (PR) or complete response (CR/CRu) upon completion of first-line chemotherapy. Randomization was stratified by center and response to first-line therapy (CR or PR). Key eligibility criteria were <25% bone marrow involvement, no prior external beam radiation or myeloablative therapy, and recovery of platelets to normal levels. Patients were randomized to receive Zevalin (n=208) or no further therapy (n=206). Y-90 Zevalin was administered at least 6 weeks but no more than 12 weeks following the last dose of chemotherapy. The main efficacy outcome measure was progression-free survival (PFS) assessed by study investigators using the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphoma (1999).
Among the 414 patients, 49% were male, 99% were Caucasian, 12% were ≥65 years old, 83% had a WHO performance status of 0, and 65% had Stage IV disease. Thirty-nine (9.5%) patients received single agent chlorambucil, 22 (5%) patients received fludarabine or a fludarabine-containing regimen, 294 (71%) patients received cyclophosphamide-containing combination chemotherapy [CHOP (31%); CHOP-like (15%); CVP/COP (26%)] and 59 (14%) patients received rituximab-containing combination chemotherapy as first-line treatment.
Progression-free survival was significantly prolonged among Zevalin-treated patients compared to those receiving no further treatment [median PFS 38 months vs. 18 months; HR 0.46 (95% CI: 0.35, 0.60) p<0.0001 Cox model stratified by response to first-line therapy and initial treatment strategy (immediate vs. watch-and-wait)]. The number of patients who died was too small to permit a reliable comparison on survival.
The results for PFS are presented in Figure 1.
[See figure 1 at top of next column]

Figure 1. Study 4: Kaplan-Meier Estimator for Investigator-Assessed Progression Free Survival Time



16 HOW SUPPLIED/STORAGE AND HANDLING

There are two kits necessary for preparation of the Zevalin therapeutic regimen: one for preparation of In-111 radiolabeled Zevalin (NDC 68152-104-04) and one for preparation of Y-90 radiolabeled Zevalin (NDC 68152-103-03). The contents of all vials are sterile, pyrogen-free, contain no preservatives, and are not radioactive. Each kit contains four identification labels and the following four vials:
1. One (1) Zevalin vial containing 3.2 mg ibritumomab tiuxetan in 2 mL 0.9% Sodium Chloride as a clear, colorless solution.
2. One (1) 50 mM Sodium Acetate Vial containing 13.6 mg Sodium Acetate trihydrate in 2 mL Water for Injection, USP as a clear, colorless solution.
3. One (1) Formulation Buffer Vial containing 750 mg Albumin (Human), 76 mg Sodium Chloride, 28 mg Sodium Phosphate Dibasic Dodecahydrate, 4 mg Pentetic Acid, 2 mg Potassium Phosphate Monobasic and 2 mg Potassium Chloride in 10 mL Water for Injection, pH 7.1 as a clear yellow to amber colored solution.
4. One (1) empty Reaction Vial.

Indium-111 Chloride Sterile Solution (In-111 Chloride) must be ordered separately from either GE Healthcare, or Mallinckrodt/Covidien.
Yttrium-90 Chloride Sterile Solution is shipped directly from the supplier upon placement of an order for the Y-90 Zevalin kit.
Rituximab (Rituxan®, Biogen Idec and Genentech USA) must be ordered separately.

Storage

Store kits at 2-8°C (36-46°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise patients:
- To contact a healthcare professional for severe signs and symptoms of infusion reactions.
- To take premedications as prescribed [*see Dosage and Administration (2.2)* and *Warnings and Precautions (5.1)*].
- To report any signs or symptoms of cytopenias (bleeding, easy bruising, petechiae or purpura, pallor, weakness or fatigue).
- To avoid medications that interfere with platelet function, except as directed by a healthcare professional [*see Warnings and Precautions (5.2)*].
- To seek prompt medical evaluation for diffuse rash, bullae, or desquamation of the skin or oral mucosa.
- To immediately report symptoms of infection (e.g. pyrexia) [*see Adverse Reactions (6.3)*].
- That immunization with live viral vaccines is not recommended for 12 months following the Zevalin therapeutic regimen [*see Warnings and Precautions (5.8)*].
- To use effective contraceptive methods during treatment and for a minimum of 12 months following Zevalin therapy.
- To discontinue nursing during and after Zevalin treatment [*see Use In Special Populations (8.3)*].

Irvine, CA 92618
U.S. License No. 1832

Stiefel Laboratories, Inc.
Research Triangle Park, NC 27709

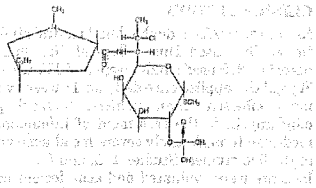
Direct Inquiries to:
Professional Services Department
1-888-STIEFEL (1-888-784-3335)

DUAC®

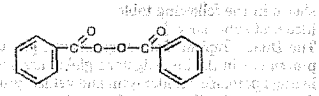
[*dū-ăk*]
(clindamycin phosphate, 1% - benzoyl peroxide, 5%)
Topical Gel
For Dermatological Use Only.
Not for Ophthalmic Use.
Rx Only

DESCRIPTION

Duac® Topical Gel contains clindamycin phosphate, (7(S)-chloro-7-deoxylincomycin-2-phosphate), equivalent to 1% clindamycin, and 5% benzoyl peroxide.
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.
Clindamycin phosphate is $C_{18}H_{34}ClN_2O_8PS$. The structural formula for clindamycin phosphate is represented below:



Clindamycin phosphate has a molecular weight of 504.97 and its chemical name 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).
Benzoyl peroxide is $C_{14}H_{10}O_4$. It has the following structural formula:



Benzoyl peroxide has a molecular weight of 242.23.
Each gram of Duac® Topical Gel contains 10 mg (1%) clindamycin, as phosphate, and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer homopolymer (type C), dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, methylparaben, poloxamer 182, purified water, silicon dioxide, and sodium hydroxide.

CLINICAL PHARMACOLOGY

A comparative study of the pharmacokinetics of Duac® Topical Gel and 1% clindamycin solution alone in 78 patients indicated that mean plasma clindamycin levels during the four week dosing period were ≤ 0.5 ng/ml for both treatment groups.
Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid.

Microbiology

Mechanism of Action

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis.
Benzoyl peroxide is a potent oxidizing agent.

***In Vivo* Activity**

No microbiology studies were conducted in the clinical trials with this product.

***In Vitro* Activity**

The clindamycin and benzoyl peroxide components individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this is not known.

Drug Resistance

There are reports of an increase of *P. acnes* resistance to clindamycin in the treatment of acne. In patients with *P. acnes* resistant to clindamycin, the clindamycin component may provide no additional benefit beyond benzoyl peroxide alone.

Mean percent reduction in inflammatory lesion counts

	Study 1 (n=120)	Study 2 (n=273)	Study 3 (n=280)	Study 4 (n=288)	Study 5 (n=358)
Duac® Topical Gel	65%	56%	42%	57%	52%
Benzoyl Peroxide	36%	37%	32%	57%	41%
Clindamycin	34%	30%	38%	49%	33%
Vehicle	19%	-0.4%	29%		29%

Local reactions with use of Duac® Topical Gel % of patients using Duac® Topical Gel with symptom present Combined results from 5 studies (n=397)

	Before Treatment (Baseline)			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

CLINICAL STUDIES

In five randomized, double-blind clinical studies of 1,319 patients, 397 used Duac® Topical Gel, 396 used benzoyl peroxide, 349 used clindamycin and 177 used vehicle. Duac® Topical Gel applied once daily for 11 weeks was significantly more effective than vehicle, benzoyl peroxide, and clindamycin in the treatment of inflammatory lesions of moderate to moderately severe facial acne vulgaris in three of the five studies (Studies 1, 2, and 5).

Patients were evaluated and acne lesions counted at each clinical visit: weeks 2, 5, 8, 11. The primary efficacy measures were the lesion counts and the investigator's global assessment evaluated at week 11. Patients were instructed to wash the face, wait 10 to 20 minutes, and then apply medication to the entire face, once daily, in the evening before retiring. Percent reductions in inflammatory lesion counts after treatment for 11 weeks in these five studies are shown in the following table:

[See first table above]

The Duac® Topical Gel group showed greater overall improvement in the investigator's global assessment than the benzoyl peroxide, clindamycin and vehicle groups in three of the five studies (Studies 1, 2, and 5).

Clinical studies have not adequately demonstrated the effectiveness of Duac® Topical Gel versus benzoyl peroxide alone in the treatment of non-inflammatory lesions of acne.

INDICATIONS AND USAGE

Duac® Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

Duac® Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS

Duac® Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or 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 *Clostridium 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 *Clostridium difficile* colitis.

PRECAUTIONS

General

For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients

Patients using Duac® Topical Gel should receive the following information and instructions:

1. Duac® Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.
4. Patients should report any signs of local adverse reactions to their physician. Patients who develop allergic symptoms such as severe swelling or shortness of breath should discontinue use and contact their physician immediately.
5. Duac® Topical Gel may bleach hair or colored fabric.
6. Duac® Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.
7. Before applying Duac® Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.
8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment. The clinical significance of this is unknown.

In a 2-year dermal cercinogenicity study in mice, treatment with Duac® Topical Gel at doses up to 8000 mg/kg/day (16 times the highest recommended adult human dose of 2.5 g Duac® Topical Gel, based on mg/m^2) did not cause an increase in skin tumors. However, topical treatment with another formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, or 2000 mg/kg/day caused a dose-dependent increase in the incidence of keratoacanthoma at the treated skin site of male rats in a 2-year dermal carinogenicity study in rats.

In a 52-week photocarcinogenicity study in hairless mice (40 weeks of treatment followed by 12 weeks of observation), the median time to onset of skin tumor formation decreased and the number of tumors per mouse increased relative to controls following chronic concurrent topical treatment with Duac® Topical Gel and exposure to ultraviolet radiation.

Genotoxicity studies were not conducted with Duac® Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Studies have not been performed with Duac® Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g Duac® Topical Gel, based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Animal reproduction studies have not been conducted with Duac® Topical Gel or benzoyl peroxide. It is also not known whether Duac® Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Duac® Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

Nursing Women

It is not known whether Duac® Topical Gel is secreted into human milk after topical application. 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 this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

[See second table above]

(Percentages derived by # subjects with symptom score/# enrolled Duac® Topical Gel subjects, n = 397).

Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in post-marketing use with Duac® Topical Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to a drug exposure.

DOSAGE AND ADMINISTRATION

Duac® Topical Gel should be applied once daily, in the evening or as directed by the physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED

Duac® (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in:

• 45 gram tube NDC 0145-2371-05

Prior to Dispensing: Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.

Dispensing Instructions for the Pharmacist: Dispense Duac® Topical Gel with a 60 day expiration date and specify "Store at room temperature up to 25°C (77°F). Do not freeze."
Keep tube tightly closed. Keep out of the reach of small children.

Stiefel Laboratories, Inc.
Research Triangle Park, NC 27709
DUA:3PI
Rev. February 2011

EVOCLIN®

℞

[ē-vō-klĭn]
(clindamycin phosphate) Foam, 1%
For Topical Use

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EVOCLIN Foam safely and effectively. See full prescribing information for EVOCLIN Foam.
EVOCLIN® (clindamycin phosphate) Foam, 1%
For Topical Use
Initial U.S. Approval: 1970

INDICATIONS AND USAGE

EVOCLIN Foam is a lincosamide product indicated for acne vulgaris in patients 12 years and older. (1)

DOSAGE AND ADMINISTRATION

- For topical use only; not for oral, ophthalmic, or intravaginal use. (2)
- Apply EVOCLIN Foam once daily to affected areas. (2)
- Flammable; avoid fire, flame and/or smoking during and immediately following application. (2)

DOSAGE FORMS AND STRENGTHS

Foam containing 1% clindamycin as clindamycin phosphate. (3)

CONTRAINDICATIONS

EVOCLIN Foam is contraindicated in individuals with a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis. (4)

WARNINGS AND PRECAUTIONS

- Colitis: Clindamycin can cause severe colitis, which may result in death. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of clindamycin. EVOCLIN Foam should be discontinued if significant diarrhea occurs. (5.1)

ADVERSE REACTIONS

The most common adverse reactions (>1%) are headache and application site reactions including burning, pruritus, and dryness. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Stiefel Laboratories, Inc. at 1-888-784-3335 (1-888-STIEFEL) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EVOCLIN Foam is indicated for topical application in the treatment of acne vulgaris in patients 12 years and older.

2 DOSAGE AND ADMINISTRATION

EVOCLIN Foam is for topical use only, and not for oral, ophthalmic, or intravaginal use.
Apply EVOCLIN Foam 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.
The contents of EVOCLIN Foam are flammable; avoid fire, flame and/or smoking during and immediately following application.

3 DOSAGE FORMS AND STRENGTHS

White to off-white thermolabile foam. Each gram of EVOCLIN Foam contains, as dispensed, 12 mg (1.2%) of clindamycin phosphate, equivalent to 10 mg (1%) of clindamycin.

4 CONTRAINDICATIONS

EVOCLIN Foam is contraindicated in individuals with a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

5 WARNINGS AND PRECAUTIONS

5.1 Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of this product. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. If significant diarrhea occurs, EVOCLIN Foam should be discontinued. [*See Adverse Reactions (6.2).*]
Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.
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. Stool cultures for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

5.2 Irritation

EVOCLIN Foam can cause irritation.
Avoid contact of EVOCLIN Foam with eyes. If contact occurs, rinse eyes thoroughly with water.
EVOCLIN Foam should be prescribed with caution in atopic individuals.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
A total of 439 subjects with mild to moderate acne vulgaris were treated once daily for 12 weeks with EVOCLIN Foam. The incidence of adverse reactions occurring in ≥1% of the subjects in clinical trials comparing EVOCLIN Foam, and its vehicle is presented in Table 1.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects

Adverse Reactions	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 Foam.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of EVOCLIN Foam: application site pain, application site erythema, diarrhea, urticaria, abdominal pain, hypersensitivity, rash, abdominal discomfort, nausea, seborrhea, application site rash, dizziness, and pain of skin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
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. Orally and parenterally administered clindamycin have been associated with severe colitis, which may end fatally.

7 DRUG INTERACTIONS

7.1 Erythromycin

EVOCLIN Foam should not be used in combination with topical or oral erythromycin-containing products due to possible antagonism to its clindamycin component. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

7.2 Neuromuscular Blocking Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women treated with EVOCLIN Foam. EVOCLIN Foam should be used during pregnancy only if the potential benefit clearly outweighs the potential risk to the fetus.
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 Foam based on a mg/m^2 comparison.

8.3 Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of EVOCLIN Foam. 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.
If used during lactation and EVOCLIN Foam is applied to the chest, care should be taken to avoid accidental ingestion by the infant.

8.4 Pediatric Use

Safety and effectiveness of EVOCLIN Foam in children under the age of 12 have not been studied.

8.5 Geriatric Use

The clinical study with EVOCLIN Foam did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently than younger subjects.

11 DESCRIPTION

EVOCLIN (clindamycin phosphate) Foam contains clindamycin (1%) as clindamycin phosphate.
Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic, lincomycin.
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). The structural formula for clindamycin phosphate is represented below:
[See chemical structure at top of next column]
Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$ Molecular Weight: 504.97 g/mol
EVOCLIN Foam contains clindamycin (1%) as clindamycin phosphate, at a concentration equivalent to 10 mg clindamycin per gram in a thermolabile hydroethanolic