

## Benefits of Combination Therapy for Acne

a report by

**Stiefel Laboratories, Inc.**

### Introduction

Acne is a rite of passage for the majority of American youth, affecting nearly 85% of all teenagers in the US.<sup>1</sup> However, unlike 50 years ago when effective treatment options were few and far between, today's teenagers have numerous over-the-counter (OTC) and prescription treatment options at their disposal.<sup>2</sup> Due to advances in the treatment of acne over past decades, it is now possible, with the proper choice of treatment, to successfully resolve nearly all cases of teenage acne.<sup>1</sup> This is especially important because uncontrolled acne can have devastating long-term consequences.<sup>2</sup> Adolescence is a critical period of emotional development, and failure to treat acne quickly and effectively can lead to problems with self-image and outlook that can last a lifetime.

### Teenagers Turn to Dermatologists

For a significant percentage of teens, acne control can be achieved using a non-medical approach, such as proper hygiene, OTC preparations, or prescription treatments provided by pediatricians or primary care physicians. However, when these measures fail, desperate teens and their parents often turn to dermatologists. For these patients, topical combinations are generally used as first-line treatment for mild to moderate acne. As Emil A. Tanghetti, Clinical Professor of Dermatology at the University of California – Davis notes:

*“Most patients with mild to moderate acne come in already having tried benzoyl peroxides or topical antibiotics as monotherapy. So, when typical over-the-counter medicines fail to control mild to moderate acne, I typically use a combination drug such as Duac® Topical Gel, which is a 5% benzoyl peroxide and 1% clindamycin combination and a topical retinoid at opposite ends of the day.”*

### Pathophysiologic Basis for Topical Treatment

The rationale for using this approach is based in the pathophysiology of acne. Inflammatory acne begins with abnormal follicular keratinization and the formation of a small keratin plug that precedes clinical comedones in the microcomedo stage.<sup>3</sup> The comedo becomes enlarged when it retains cellular debris. Dilatation of the follicular opening occurs and a blackhead may form. Plugged sebaceous materials create the ideal condition for colonization of the follicle by the anaerobic organism *Propionibacterium acnes*, which promotes inflammation.<sup>2</sup>

Dr Tanghetti, linking the pathophysiology of acne to his choices for topical treatments, explains:

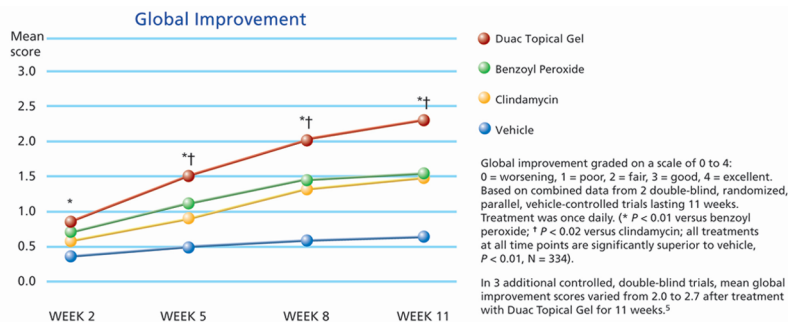
*“The retinoid unplugs the pores and the topical combination of benzoyl peroxide-clindamycin exerts antibacterial and anti-inflammatory effects. It is also shown that a combination agent, such as Duac Topical Gel, enhances comedial lysis, which, in turn, enhances the activity of the retinoid. Topical combinations seem to do a better job than single agents because you spare toxicities by using these drugs in combination.”*

A topical combination like Duac Topical Gel is also appropriate as initial treatment without a retinoid. Joseph B. Bikowski, Director of the Bikowski Skin Care Center in Sewickley, Pennsylvania, notes that he has found the combination of benzoyl peroxide and clindamycin a very effective starting point in acne treatment.

*“There are studies that show that benzoyl peroxide in combination with clindamycin is effective not only for inflammatory lesions, but also for open and closed comedones. So, for patients who are intolerant of topical retinoids or who have had difficulties with retinoids in the past, starting from day one with benzoyl peroxide in combination with clindamycin is a good strategy.”*

1. Honig P J, “Treating acne: choosing the right agent”, *Infect Dis. Child. September 2004*: pp. 7–9.
2. Berson D S, Chalker D K, Harper J C, Leyden J J, Shalita A R and Webster GF, “Current concepts in the treatment of acne: report from a clinical roundtable”, *Cutis. (2003), 72*: pp. 5–13.
3. Eichenfield L, “Acne pathophysiology: a biological review”, *Infect Dis. Child. September 2004*: pp. 4–5.



Figure 1: Global Improvement<sup>4</sup>

The efficacy of benzoyl peroxide topical combinations is well established.<sup>1</sup> It is founded on the remarkable antimicrobial action of benzoyl peroxide. As Dr Bikowski notes, “topical benzoyl peroxide is the most effective way to decrease the *P. acnes* count ... it’s the best topical microbial that we have.” When benzoyl peroxide is combined with the proven topical antibiotic clindamycin – the combination found in Duac Topical Gel – the synergy between the two translates to fast and effective relief of inflammatory acne. One study demonstrated significant global improvement as early as week two (see Figure 1).<sup>4</sup>

### Topical Combination Treatments in the Era of Growing Antimicrobial Resistance

After recent increases in antimicrobial resistance, possibly linked to decades of widespread use of systemic antibiotics, the dermatology community has begun to shift its approach to acne treatment. Dr Bikowski explains:

*“We have seen resistance with *P. acnes* to the systemic antibiotics, and possibly topical antibiotics, and growth in resistance among other bacteria, possibly produced by the widespread use of systemic antibiotics to treat acne. This has resulted in a paradigm shift in acne therapy away from systemic antibiotics alone or in combination with topicals, to topicals alone and in combination.”*

Dr Tanghetti emphasizes the increasingly important role that combination products like Duac Topical Gel play in the era of resistance:

*“It is my belief that if we use topical drugs in combination and use oral treatments only when we really need them, we can slow the growth of resistance. That is why I use topical combinations such as Duac Topical Gel. Topical combination therapy for acne is something of paramount importance in the era of resistance.”*

### Compliance – the Necessary Ingredient in Successful Teenage Acne Management

Regardless of how efficacious an acne treatment may be, if the teenage patient fails to use it as prescribed, it will do little good. Dr Tanghetti observes that the typical teen patient may have the best of intentions, but good intentions often fail to translate into action.

*“Teenage patients are very difficult. They are always in a hurry, they are dealing with emotional issues, and they often don’t make the time to follow through with treatment. So, making the treatment regimen practical for the teen’s busy life is perhaps the most challenging issue. Selecting a combination product that offers qd dosing, such as Duac Topical Gel, is an important key to encouraging compliance in the teen patient.”*

Tolerability also plays an important role in compliance with acne treatment and depends on a number of factors, including irritability, cosmetic elegance, and moisturizing and cleansing practices. According to Dr Tanghetti, a topical combination that is formulated with the emollients dimethicone and glycerin, such as Duac Topical Gel, can be less irritating and much more compatible with the use of topical retinoids (applied at a different time in the day). These emollients also make the product cosmetically elegant, which can enhance compliance. “Teens won’t use a product that cakes on or leaves a residue or odor.”

Proper washing and moisturizing are also an important part of ensuring the tolerability of acne treatments by keeping the skin from drying and cracking. “I have my teenage patients pay strict attention to barrier function. That means avoiding use of soap products that will strip the lipids from the epidermis. So I typically have them use nonsoap cleansers.”

Finally, as Dr Bikowski reminds us, ease of use tends to encourage compliance.

*“A product like Duac Topical Gel comes in a tube and is simple and easy to use. This gives it an advantage over other combination products. With Duac Topical Gel, you can squeeze out just the amount you need. It’s much more difficult to get the correct amount out of a jar. And because the jar contents are mixed at the pharmacy, the consistency sometimes can be gritty and it can be inconsistent because of the different compounding skills of the given pharmacist.”*

4. Lookingbill D P, Chalker D K, Lindholm J S, et al., “Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations”, *J. Am. Acad. Dermatol.* (1997), 37: pp. 590–595.

5. Data on file, August C. Stiefel Research Institute, Inc.

**Answering the Call with  
DUAC Topical Gel**

Inflammatory acne may be a right of passage for American teenagers, but with the advent of easy-to-use, once-a-day topical combinations such as Duac Topical Gel, it can be an easy passage. The active ingredients in Duac Topical Gel work in synergy to provide fast and powerful relief of inflammatory acne. Just as important, Duac Topical Gel is designed to fit the teenage lifestyle, with once-a-day dosing (preferred by 87% of patients) and a gentle, water-based, alcohol- and fragrance-free formulation containing the emollients dimethicone and glycerin.<sup>6</sup> It's no wonder that Duac Topical Gel is the fastest-growing acne medication in the US with over one million prescriptions and counting.<sup>7</sup>

Duac Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin, and in those with a history of regional enteritis, ulcerative colitis, pseudomembranous colitis,

*Fastest-growing acne medication in the US – over  
1 million Rx's strong<sup>7</sup>*



or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. Discontinuation is recommended if significant diarrhea develops. ■

*Please see the following full Prescribing Information. For more information about Duac Topical Gel or Stiefel Laboratories, Inc., visit [www.duacgel.com](http://www.duacgel.com) and [www.stiefel.com](http://www.stiefel.com)*

6. Data on file, Stiefel Laboratories, Inc.

7. IMS data, July 2004.

# Duac<sup>®</sup> Topical Gel

(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.  
Not for Ophthalmic Use.

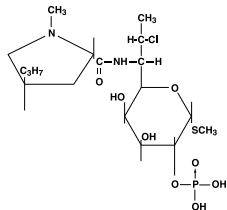
## Rx Only

### DESCRIPTION

Duac<sup>®</sup> Topical Gel contains clindamycin phosphate, (7(S)-chloro-7-deoxylincomycin-2-phosphate), equivalent to 1% clindamycin, and 5% benzoyl peroxide.

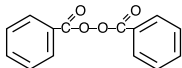
Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

Clindamycin phosphate is C<sub>18</sub>H<sub>34</sub>ClN<sub>2</sub>O<sub>8</sub>PS. 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-pyrrolidinedicarboxamido)-1-thio-L-*threo*- $\alpha$ -D-galacto-octopyranoside 2-(dihydrogen phosphate).

Benzoyl peroxide is C<sub>14</sub>H<sub>10</sub>O<sub>4</sub>. 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 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methylparaben, poloxamer, purified water, 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.

### CLINICAL STUDIES

In five randomized, double-blind clinical studies of 1,319 patients, 397 used Duac, 396 used benzoyl peroxide, 349 used clindamycin and 177 used vehicle. Duac 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:

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	65%	56%	42%	57%	52%
Benzoyl Peroxide	36%	37%	32%	57%	41%
Clindamycin	34%	30%	38%	49%	33%
Vehicle	19%	-0.4%	29%		29%

The Duac 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 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.
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. The clinical significance of this is unknown.

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.

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<sup>2</sup>) 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<sup>2</sup>, 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<sup>2</sup>, 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:

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

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

**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 a 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.

U.S. Patent Nos. 5,466,446, 5,446,028, 5,767,098, and 6,013,637  
Patents Pending



Stiefel Laboratories, Inc.  
Coral Gables, FL 33134

813582 Rev. 0104