

Effective Treatment Strategies in the Management of Acne

Focus on Adult Females

A Roundtable Discussion

Sponsored by Valeant
Pharmaceuticals North America LLC.

Supplement to



- **DIANE BERSON, MD, CHAIR**
- **ANDREW ALEXIS, MD**
- **HILARY BALDWIN, MD**
- **RICHARD FRIED, MD, PHD**
- **LINDA STEIN GOLD, MD**

In recent years, adult female acne has been the subject of increased inquiry in research and in clinical practice. In particular, new data have elucidated both the prevalence and clinical characteristics of acne for adult female patients. Therefore, effective treatment strategies to address the scope of adult female acne are paramount for clinicians. In this roundtable discussion, experts offer strategies and pearls for treatment. In particular, they discuss the role of clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel (Onexton, Valeant Pharmaceuticals), a formulation approved in 2014, in the growing treatment armamentarium.

“As clinicians and researchers continue to delve deeper into the variety of factors contributing to adult female acne, several distinctive traits have emerged.”

THE IMPACT OF ACNE IN ADULT FEMALE PATIENTS

Although the public perception is that acne is a minor skin condition that affects primarily adolescents, the reality is much more nuanced, according to the panelists. “Many feel that acne is a condition that affects only teens, and that most will eventually grow out of it in adulthood,” says Dr. Berson. But data have increasingly indicated that acne affects adults, as well, with a higher prevalence in women than men.¹⁻⁴ In fact, the incidence of acne in adult females has been reported at 51 percent in women between the ages of 20 and 29 years, decreasing over time to 15.3 percent for women over 50 years old.⁴ Additionally, roughly 80 percent of acne in females is classified as persistent (adolescent onset but per-

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sistent in adulthood) and 20 percent as late-onset.⁴ “This is not just a trite condition,” says Dr. Berson. The broad perception of acne as an adolescent condition can make it especially challenging for adults, according to Dr. Stein Gold.

Although historically many therapies have not been targeted for the adult acne patient, notes Dr. Berson, adult female acne has received greater attention in recent years. Additionally, several roundtable contributors report that adult female acne is on the rise in their practices. “Acne is my number one diagnosis among adults,” says Dr. Alexis. “And among those adults, my typical patient is over 30 years old and female.”

Dr. Baldwin has also seen more adult female patients and believes that a variety of factors may be contributing to the phenomenon. “The data currently do not support an increase in the incidence of adult females with acne,” says Dr. Baldwin. “Some women come in to have their kids treated and they discover that acne medication is better now than when they were kids and maybe now it’s time for them to finally do something about it,” she adds.

Dr. Stein Gold agrees that increased awareness for both the condition and therapies is playing a key role. “Perhaps with the increase in direct to consumer advertising targeting adult women, people are being spurred on more to come in now,” says Dr. Stein Gold. An investigator in many acne studies over the last several years, Dr. Stein Gold observes that adult females have always been substantial in the acne population. “Maybe women have persistent acne and they have become fed up. With newer drugs and more directed messages towards women, they’re now coming to the office,” says Dr. Stein Gold.

Yet, while the increased visibility of adult female acne has fostered more awareness, it doesn’t always translate to patients receiving better treatment, according to Dr. Stein Gold. Moreover, even with an increase in interest and therapeutic options for adult female populations, Dr. Fried notes that patients are coming to practices with different needs and expectations, which can complicate treatment approaches.

CLINICAL CHARACTERISTICS OF ADULT FEMALE ACNE

As clinicians and researchers continue to delve deeper into the variety of factors contributing to adult female acne, several distinctive traits have emerged. In particular, distribution patterns and types of acne in adult female patients has until recently been a subject of some discord. “The traditional thought is that adolescent acne occurs in the T-zone and is mostly comedonal—with oil and clogging—and that adult female acne develops in the U-distribution on the cheeks, the jaw line, the chin and the neck and is more inflammatory,” says Dr. Berson.

However, new research challenges these notions. In particular, Dreno, et al. found that the acne distribution in almost 90 percent of cases is similar to that seen in adolescent acne.³ Moreover, the authors found that 93.7 percent of women had facial comedones, with the most common presentation of acne as neither inflammatory or non-inflammatory alone but mixed. Erythema was present in 41.4 percent of patients and it was most frequently observed in patients between the age of 25 and 30 years old. Moreover, it occurred with decreasing frequency in older age groups in both males and females. The researchers also observed that 25 percent of patients had both post-inflammatory hyperpigmentation (PIH) and erythema present.³

The investigators also examined the proportion of patients with acne lesions on the mandibular area but no other facial areas and found that 11.2 percent of women had acne lesions localized to the mandibular area. They further noted that truncal involvement was present in just under half of the patients, with nodules reported in 14.2 percent of the women with similar frequencies on the cheeks and mandibular area but less common on the forehead or temple.³

Dr. Alexis has made similar observations in his own studies in this population. “When doing my lesion counts in a recent phase IV study, I never encountered a situation where I didn’t meet the comedone requirement in the adult female population,” says Dr. Alexis. “The number of comedones

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was just as high as I would expect them to be in younger age groups and males as well,” explains Dr. Alexis. “When looking at it more objectively and thinking about my adult female patients, I realized that comedones are still quite a common component of their acne too,” he says.

“Most of the women that I see have acne all over their face,” says Dr. Baldwin. “But there certainly is a subset of jaw-line, inflammatory-only, non-comedonal acne. These patients have never been studied specifically and we have no data behind their treatment protocols,” Dr. Baldwin continues. Says Dr. Berson, “We all have seen a subset of women who have the classic inflammatory, cystic, neck and jaw acne,” she says. “It exists, as the Dreno findings suggest, and there is probably a hormonal component to that,” says Dr. Berson.

Given recent findings regarding the type and distribution of acne, a persisting question is whether adult female acne is more difficult to treat. Dr. Stein Gold notes that in the trials she has conducted, they have evaluated the efficacy of various topical agents and that the data are mostly consistent with what we see within the population as a whole.

Dr. Berson adds that some of these patients may actually be easier to treat in some respects. “In these women, we can take advantage of hormonal therapy as an adjunct to the other treatments that we don’t use in males and even in some of the younger girls,” says Dr. Berson. Cystic acne, however, can be more difficult. These patients are more likely to have recurring acne even after isotretinoin treatment, says Dr. Berson.

Dr. Stein Gold implores that when you look at adult women, especially with severe acne or difficult to control, you have to look at all the underlying issues, as well. “Is there a hormonal abnormality that we’re missing? Is there polycystic ovarian syndrome that has never been diagnosed?”

Dr. Berson says that hormonal abnormalities or influences can indeed exist in many of these patients and that taking a good history is essential. “And while we may add hormonal treatments as an adjunct in these cases, we still tend to use traditional therapies for these women,” says Dr. Berson. Adds

“Perhaps with the increase in direct to consumer advertising targeting adult women, people are being spurred on more to come in now... Maybe women have persistent acne and they have become fed up. With newer drugs and more directed messages towards women, they’re now coming to the office.”

—Dr. Stein Gold.

Dr. Stein Gold, “Hormonal therapy is not first-line. It’s an adjunct.”

Hormonal intervention has become more mainstream, though its main benefit is to help prevent new breakouts, according to Dr. Berson. “It does not address existing acne and therefore it is not a first line treatment,” says Dr. Berson.

ONEXTON (CLINDAMYCIN PHOSPHATE AND BENZOYL PEROXIDE) GEL, 1.2%/3.75%

Approved by the Food and Drug Administration (FDA) in 2014, the combination formulation clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel (Onexton, Valeant Pharmaceuticals) is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.⁵

“In addition to containing benzoyl peroxide, which has antimicrobial and keratolytic properties, it also contains clindamycin, which is anti-inflammatory due to the reduction of *Propionibacterium acnes* (*P. acnes*) and is readily absorbed,” says Dr. Berson. “Therefore, it targets three out of the four pathogenic factors of acne.” She adds that since comedones are part of the clinical acne presentation of

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Onexton in Adolescent Acne

Data indicate that clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel is an appropriate choice for many adolescents with moderate-to-severe acne, with favorable efficacy and tolerability profiles.¹ A post-hoc analysis of efficacy and cutaneous tolerability was performed in 289 adolescents (age range, 12 to 18 years) with moderate-to-severe acne. The patients were randomized to receive either clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel or vehicle once daily for 12 weeks.

In the clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel group, mean reduction in inflammatory lesions and noninflammatory lesions was 59.9 percent and 50.5 percent, respectively, as compared to 22.6 percent and 21.3 percent in the vehicle arm, respectively ($P < 0.001$). Additionally, one-third of patients

treated with clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel achieved greater than two-grade improvement from baseline in their Evaluator's Global Severity Score (compared to 8.5 percent with vehicle) ($P < 0.001$). Moreover, 35 percent of patients reported clear or almost clear skin at 12 weeks (compared to 12.8 percent with vehicle) according to the author. Cutaneous tolerability was also described as "excellent." The most common local adverse reactions in clinical trials, occurring in less than 0.05% of patients, were mild to moderate erythema, scaling, itching, burning, and stinging.

Please see Prescribing Information on following pages.

1. Cook-Bolden, FE. Efficacy and Tolerability of a Fixed Combination of Clindamycin Phosphate (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Moderate or Severe Adolescent Acne Vulgaris. *J Clin Aesth Dermatol*. May 2015. 8: 28-32

adult female acne, having an agent that is keratolytic or comedolytic in addition to being antimicrobial is especially beneficial.

Dr. Berson notes that the benzoyl peroxide is micronized, meaning that 90 percent of the particles are less than 10 microns in diameter. Additionally, she explains, the clindamycin is water-soluble and it's also fully dissolved in the vehicle. "So we get great delivery of the two active ingredients," says Dr. Berson.

It's also important to note that the product has a humectant with hydrating properties and an aqueous gel, says Dr. Berson. "It is alcohol-free and contains no surfactants or preservatives, and the pH ranges from 5 to 6 for acne-prone skin." These factors are important given the role vehicles play in the penetration of any topical agent, observes Dr. Baldwin.

Clinical Data. Clinical data offer a compelling account for the role of clindamycin phosphate 1.2%/benzoyl peroxide 3.75% in the therapeutic

"In my practice, the response has been favorable from patients thus far," Dr. Alexis says. Dr. Baldwin echoes that experience. "I haven't had any irritancy callbacks, which is in keeping with the data," Dr. Baldwin says.

armamentarium for acne,⁶⁻⁸ including adult female acne.^{6,8} In a randomized, double-blind study, 498 patients between the ages of 12 and 40 were randomized to receive clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel or a vehicle for 12 weeks.⁶ Dr. Baldwin notes, "The absolute change in the comedonal lesions was 19.2 versus 9.6 for vehicle, but also looking at the absolute change in inflammatory lesion counts, 16.3 versus 8.2, both of

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“The role for this product is clear based on the fact that it reduces inflammatory and comedonal lesions and it shows great efficacy and cutaneous tolerability.”

—Dr. Berson

those being statistically significant,” says Dr. Baldwin. The co-primary endpoint was the proportion of subjects who achieved at least a 2-grade reduction from Baseline at Week 12 in the EGSS, which was 35 percent versus 17 percent with the vehicle.⁶

A post-hoc analysis evaluating women 25 years of age or older showed a greater reduction across the board in inflammatory/non-inflammatory acne and an increase in overall success rate.⁸ “There was a 60 percent mean reduction in comedonal lesions compared to 34 percent for controls, and a 69 percent mean reduction from baseline in inflammatory lesions compared to 40 percent for controls,” said Dr. Baldwin, noting that the women appeared to respond better to treatment.

While the efficacy of the product is worth noting with respect to both inflammatory and non-inflammatory lesions, the tolerability data are equally significant, according to Dr. Berson. The most common local adverse events, seen in less than 0.05% of patients, were mild to moderate erythema, scaling, itching, burning and stinging. “I don’t think we can get that with an inactive vehicle,” says Dr. Fried. Additionally, in the clindamycin 1.2%/benzoyl peroxide 3.75% group, more than 80 percent of patients had no erythema, and mean erythema scores were the same in both treatment groups.⁶ Also, less than 12 percent of patients had scaling, less than 13 percent had itching, and less than five percent had stinging or burning at week 12.

In total, treatment related adverse events occurred in less than two percent of patients. Onexton is contraindicated in patients with known hypersen-

sitivity to clindamycin, BPO, any component of the formulation, or lincomycin. It is also contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

Real-World Use. The strong efficacy and cutaneous tolerability data for clindamycin phosphate 1.2%/benzoyl peroxide 3.75% are reflected in patient response, according to Dr. Alexis. “In my practice, the response has been favorable from patients thus far,” Dr. Alexis says. Dr. Baldwin echoes that experience. “I haven’t had any irritancy callbacks, which is in keeping with the data,” Dr. Baldwin says. Dr. Alexis also points out that this is particularly interesting given the location of his practice. “Climates are pretty cold in the winter months in the Northeast, and even still we’re seeing little complaints of irritation from patients,” he says.

From a broader point of view, Dr. Berson feels that the tolerability profile for this agent is especially significant in light of the high volume of acne cases that dermatologists are accustomed to seeing in practice. Additionally, Dr. Fried points out that the strong tolerability data are notable because physicians are under more pressure than ever to find an agent that “plays well” with other agents and is cosmetically formulated. “Many patients I have observed take issue with any sign of irritation, any sign that they perceive as being allergy, they perceive as being bothersome,” says Dr. Fried. “This is especially important in the adult female who may have dryness, sensitive skin, or photodamage,” says Dr. Berson.

Thus, the favorable tolerability profile and compatibility with skin care regimens is essential, she notes. If a patient develops symptoms of an allergic reaction such as swelling and shortness of breath, they should be instructed to discontinue use and contact the physician immediately, as anaphylaxis has been reported in post-marketing use of clindamycin/BPO products.

Additionally, from a practical standpoint, the fact that a significant population of patients with moderate to severe acne who used the product as a monotherapy became clear or almost clear is especially favorable given that it is a once-daily product,

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says Dr. Berson, which patients often identify as a benefit. Moreover, the fixed dose can be particularly beneficial, says Dr. Stein Gold. “I always prefer a fixed combination because it puts the power in my hands. If you give patients many things to do, the power is in their hands.”

It is also worth noting that multi-drug acne regimens are common, including those that would include a clindamycin/benzoyl peroxide combination, according to Dr. Berson. “This can be beneficial for the adult female with both acne and photodamage,” says Dr. Berson. “And you might use hormonal therapy as an adjunct, depending on the individual situation.”

Onexton should not be used in combination with erythromycin-containing products because of its clindamycin component. Additionally, Onexton should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and the decision should be made whether to use Onexton while nursing, taking into account the importance of the drug to the mother. Patients should be instructed to wear sunscreen and protective clothing and avoid sunlamps and UVA/B treatment while using Onexton.

CONCLUSION

Dr. Fried notes that the unique clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel combination is a valuable addition to the therapeutic arsenal. Moreover, he believes that this product will play an important role in the evolving spectrum of acne treatment. Dr. Berson shares that belief. “The role for this product is clear based on the fact that it reduces inflammatory and comedonal lesions and it shows great efficacy and cutaneous tolerability,” Dr. Berson concludes. ■

Please see Prescribing Information on following pages.

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Linda Stein Gold, MD, is Director of Dermatology Clinical Research at Henry Ford Health System in Detroit, Michigan, as well as Division Head of Dermatology at Henry Ford Health System in West Bloomfield, Michigan.



1. Cunliffe, WJ, Gould DJ. Prevalence of acne vulgaris in late adolescence and in adults. *British Medical Journal*. April 28, 1979
2. Goodman, G. Acne: Natural history, facts and myths. *Australian Family Physician*. 2006. 25(8): 613-616.
3. Dreno et al. Large-scale international study enhance understanding of an emerging acne population: adult females. *J EADV*. 2014.
4. Holzmann R, Shakery K. Postadolescent Acne in Females. *Skin Pharmacol Physiol*. 2014; 27 (suppl 1): 3-8.
5. Prescribing Information. Onexton (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75%.
6. Pariser D, et al. An Aqueous Gel Fixed Combination of Clindamycin Phosphate 1.2% and Benzoyl Peroxide 3.75% for the Once-Daily Treatment of Moderate to Severe Acne Vulgaris. *Journal of Drugs in Dermatology*. September 2014.(13); 9: 611-617.
7. Cook-Bolden, FE. Efficacy and Tolerability of a Fixed Combination of Clindamycin Phosphate (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Moderate or Severe Adolescent Acne Vulgaris. *J Clin Aesth Dermatol*. May 2015. 8: 28-32.
8. Zeichner, J. The Efficacy and Tolerability of a Fixed Combination Clindamycin (1.2%) and Benzoyl Peroxide (3.75%) Aqueous Gel in Adult Female Patients with Facial Acne Vulgaris. *J Clin Aesthet Dermatol*. 2015 Apr;8(4): 21-5.
9. Data on File. Valeant Pharmaceuticals.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONEXTON Gel safely and effectively. See full prescribing information for ONEXTON Gel.

ONEXTON™ (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% for topical use
Initial U.S. Approval: 2000

INDICATIONS AND USAGE

ONEXTON Gel is a combination of clindamycin phosphate (a lincosamide antibacterial) and benzoyl peroxide indicated for the topical treatment of acne vulgaris in patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Apply a pea-sized amount of ONEXTON Gel to the face once daily. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Gel, 1.2%/3.75%

Each gram of ONEXTON Gel contains 12 mg (1.2%) clindamycin phosphate, equivalent to 10 mg (1%) clindamycin, and 37.5 mg (3.75%) benzoyl peroxide. (3)

CONTRAINDICATIONS

ONEXTON Gel is contraindicated in:

- Patients who have demonstrated hypersensitivity (e.g., anaphylaxis) to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. (4.1)

- Patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. (4.2)

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. ONEXTON Gel should be discontinued if significant diarrhea occurs. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize sun exposure following drug application. (5.2)

ADVERSE REACTIONS

- The most common adverse reactions are: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- ONEXTON Gel should not be used in combination with erythromycin-containing products because of its clindamycin component. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ONEXTON™ (clindamycin phosphate and benzoyl peroxide) Gel, 1.2%/3.75% is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

Before applying ONEXTON Gel, wash the face gently with a mild soap, rinse with warm water, and pat the skin dry. Apply a pea-sized amount of ONEXTON Gel to the face once daily. Avoid the eyes, mouth, lips, mucous membranes, or areas of broken skin.

Use of ONEXTON Gel beyond 12 weeks has not been evaluated.

ONEXTON Gel is not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Gel, 1.2%/3.75%

Each gram of ONEXTON Gel contains 12 mg (1.2%) clindamycin phosphate, equivalent to 10 mg (1%) clindamycin, and 37.5 mg (3.75%) benzoyl peroxide in a white to off-white, opaque, smooth gel.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

ONEXTON Gel is contraindicated in those individuals who have shown hypersensitivity to clindamycin, benzoyl peroxide, any components of the formulation, or lincomycin. Anaphylaxis, as well as allergic reactions leading to hospitalization, has been reported in postmarketing use with ONEXTON Gel [see *Adverse Reactions* (6.2)].

4.2 Colitis/Enteritis

ONEXTON Gel is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis [see *Warnings and Precautions* (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of clindamycin. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic clindamycin. If significant diarrhea occurs, ONEXTON Gel should be discontinued.

Severe colitis has occurred following oral and 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 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 Ultraviolet Light and Environmental Exposure

Minimize sun exposure (including use of tanning beds or sun lamps) following drug application [see *Nonclinical Toxicology* (13.1)].

6 ADVERSE REACTIONS

The following adverse reaction is described in more detail in the *Warnings and Precautions* section of the label:

- Colitis [see *Warnings and Precautions* (5.1)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates observed in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

These adverse reactions occurred in less than 0.5% of subjects treated with ONEXTON Gel: burning sensation (0.4%); contact dermatitis (0.4%); pruritus (0.4%); and rash (0.4%).

During the clinical trial, subjects were assessed for local cutaneous signs and symptoms of erythema, scaling, itching, burning and stinging. Most local skin reactions either were the same as baseline or increased and peaked around week 4 and were near or improved

from baseline levels by week 12. The percentage of subjects that had symptoms present before treatment (at baseline), during treatment, and the percent with symptoms present at week 12 are shown in Table 1.

Table 1: Local Skin Reactions - Percent of Subjects with Symptoms Present. Results from the Phase 3 Trial of ONEXTON Gel 1.2%/3.75% (N = 243)

	Before Treatment (Baseline)			During Treatment			End of Treatment (Week 12)		
	Mild	Mod.*	Severe	Mild	Mod.*	Severe	Mild	Mod.*	Severe
Erythema	20	6	0	26	5	<1	15	2	0
Scaling	10	1	0	19	3	0	10	<1	0
Itching	14	3	<1	15	3	0	7	2	0
Burning	5	<1	<1	7	1	<1	3	<1	0
Stinging	5	<1	0	7	0	<1	3	0	<1

*Mod. = Moderate

6.2 Postmarketing Experience

Because postmarketing adverse 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.

Anaphylaxis, as well as allergic reactions leading to hospitalizations, has been reported in postmarketing use of products containing clindamycin phosphate/benzoyl peroxide.

7 DRUG INTERACTIONS

7.1 Erythromycin

Avoid using ONEXTON Gel in combination with topical or oral erythromycin-containing products due to its clindamycin component. *In vitro* studies have shown antagonism between erythromycin and clindamycin. The clinical significance of this *in vitro* antagonism is not known.

7.2 Concomitant Topical Medications

Concomitant topical acne therapy should be used with caution since a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents. If irritancy or dermatitis occurs, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

7.3 Neuromuscular Blocking Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women treated with ONEXTON Gel. ONEXTON Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproductive/developmental toxicity studies have not been conducted with ONEXTON Gel or benzoyl peroxide. Developmental toxicity studies of clindamycin performed in rats and mice using oral doses of up to 600 mg/kg/day (240 and 120 times amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of up to 200 mg/kg/day (80 and 40 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

8.3 Nursing Mothers

It is not known whether clindamycin is excreted in human milk after topical application of ONEXTON Gel. 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 use ONEXTON Gel while nursing, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ONEXTON Gel in pediatric patients under the age of 12 years have not been evaluated.

8.5 Geriatric Use

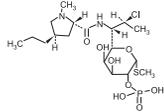
Clinical trials of ONEXTON Gel did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

ONEXTON Gel is a combination product with two active ingredients in a white to off-white, opaque, smooth, aqueous gel formulation intended for topical use. Clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(1R)-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:

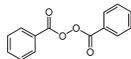
Clindamycin phosphate:



Molecular Formula: C₁₈H₃₄ClN₂O₈PS Molecular Weight: 504.97

Benzoyl peroxide is an antibacterial and keratolytic agent. The structural formula for benzoyl peroxide is represented below:

Benzoyl peroxide:



Molecular Formula: C₁₄H₁₀O₂ Molecular Weight: 242.23

ONEXTON Gel contains the following inactive ingredients: carbomer 980, potassium hydroxide, propylene glycol, and purified water. Each gram of ONEXTON Gel contains 12 mg (1.2%) clindamycin phosphate, equivalent to 10 mg (1%) clindamycin, and 37.5 mg (3.75%) benzoyl peroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clindamycin: Clindamycin is a lincosamide antibacterial [see *Clinical Pharmacology* (12.4)].

Benzoyl Peroxide: Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects, but the precise mechanism of action is unknown.

12.3 Pharmacokinetics

The systemic absorption of ONEXTON Gel has not been evaluated. The systemic absorption of clindamycin was investigated in an open-label, multiple-dose trial in 16 adult subjects with moderate to severe acne vulgaris treated with 1 gram of a marketed gel containing clindamycin 1%/benzoyl peroxide 2.5% applied to the face once daily for 30 days. This product has the same formulation as ONEXTON Gel but with a lower concentration of benzoyl peroxide. Twelve subjects (75%) had at least one quantifiable clindamycin plasma concentration above the lower limit of quantification (LOQ = 0.5 ng/mL) on Day 1 or Day 30. On Day 1, the mean (± standard deviation) peak plasma concentrations (C_{max}) was 0.78 ± 0.22 ng/mL (n=9 with measurable concentrations), and the mean AUC₀₋₂₄ was 5.29 ± 0.81 h·ng/mL (n=4). On Day 30, the mean C_{max} was 1.22 ± 0.88 ng/mL (n=10), and the mean AUC₀₋₂₄ was 8.42 ± 6.01 h·ng/mL (n=6). Clindamycin plasma concentrations were below LOQ in all subjects at 24 hours post-dose on the three tested days (Day 1, 15, and 30).

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid.

12.4 Microbiology

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation of peptide chains by interfering with peptidyl transfer, thereby suppressing bacterial protein synthesis.

Clindamycin and benzoyl peroxide individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris. In an *in vitro* study, the MIC for benzoyl peroxide against *Propionibacterium acnes* is 128 mg/L. The clinical significance of this activity against *P. acnes* is not known.

P. acnes resistance to clindamycin has been documented. Resistance to clindamycin is often associated with resistance to erythromycin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity and impairment of fertility testing of ONEXTON Gel have not been performed.

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 topically twice per week for 20 weeks induced skin tumors in transgenic Tg.AC mice. The clinical significance of this is unknown.

Carcinogenicity studies have been conducted with a gel formulation containing 1% clindamycin and 5% benzoyl peroxide. In a 2-year dermal carcinogenicity study in mice, treatment with the gel formulation at doses of 900, 2700, and 15000 mg/kg/day (1.8, 5.4, and 30 times amount of clindamycin and 2.4, 7.2, and 40 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m², respectively) did not cause any increase in tumors. However, topical treatment with a different gel formulation containing 1% clindamycin and 5% benzoyl peroxide at doses of 100, 500, and 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 carcinogenicity study in rats. In an oral (gavage) carcinogenicity study in rats, treatment with the gel formulation at doses of 300, 900 and 3000 mg/kg/day (1.2, 3.6, and 12 times amount of clindamycin and 1.6, 4.8, and 16 times amount of benzoyl peroxide in the highest recommended adult human dose of 2.5 g ONEXTON Gel based on mg/m², respectively) for up to 97 weeks did not cause any increase in tumors. In a 52-week dermal 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 administration of the higher concentration benzoyl peroxide formulation (5000 and 10000 mg/kg/day, 5 days/week) and exposure to ultraviolet radiation.

Clindamycin phosphate was not genotoxic in the human lymphocyte chromosome aberration assay. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *S. typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

Fertility studies have not been performed with ONEXTON Gel or benzoyl peroxide, but fertility and mating ability have been studied with clindamycin. 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 ONEXTON Gel, based on mg/m²) revealed no effects on fertility or mating ability.

14 CLINICAL STUDIES

The safety and efficacy of once daily use of ONEXTON Gel was assessed in a 12-week multi-center, randomized, blinded trial in subjects 12 years and older with moderate to severe acne vulgaris. This trial evaluated ONEXTON Gel compared to vehicle gel.

The co-primary efficacy variables for this trial were:

(1) Mean absolute change from baseline at week 12 in

- Inflammatory lesion counts
- Non-inflammatory lesion counts

(2) Percent of subjects who had a two grade reduction from baseline on an Evaluator's Global Severity (EGS) score.

The EGS scoring scale used in the clinical trial for ONEXTON Gel is as follows:

Table 2: EGS Scoring Scale

Grade	Description
Clear	Normal, clear skin with no evidence of acne
Almost Clear	Rare non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
Mild	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
Moderate	Non-inflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion
Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be up to 2 nodulocystic lesions
Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and more than 2 nodulocystic lesions

The results of the trial at Week 12 are presented in Table 3:

Table 3: Results of Phase 3 Trial with ONEXTON Gel 1.2%/3.75% at Week 12

	ONEXTON Gel N = 253	Vehicle Gel N = 245
EGSS:		
Clear or Almost Clear	29%	15%
2-grade reduction from baseline	35%	17%
Inflammatory Lesions:		
Mean absolute reduction	16.3	8.2
Mean percent (%) reduction	60.4%	31.3%
Non-inflammatory Lesions:		
Mean absolute reduction	19.2	9.6
Mean percent (%) reduction	51.8%	27.6%

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ONEXTON Gel 1.2%/3.75% is a white to off-white smooth gel supplied as a 50 g pump (NDC 0187-3050-50)

16.2 Dispensing Instructions for the Pharmacist

- Dispense ONEXTON Gel with a 10 week expiration date.
- Specify "Store at room temperature up to 25°C (77°F). Do not freeze."

16.3 Storage and Handling

- PHARMACIST: Prior to Dispensing: Store in a refrigerator, 2°C to 8°C (36°F to 46°F).
- PATIENT: Store at room temperature at or below 25°C (77°F).
- Protect from freezing.
- Store pump upright.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

- Patients who develop allergic reactions such as severe swelling or shortness of breath should discontinue use and contact their physician immediately.
- ONEXTON Gel may cause irritation such as erythema, scaling, itching, or burning, especially when used in combination with other topical acne therapies.
- Patients should limit excessive or prolonged exposure to sunlight. To minimize exposure to sunlight, a hat or other clothing should be worn. Sunscreen may also be used.
- ONEXTON Gel may bleach hair or colored fabric.

Manufactured for:

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Made in Canada

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