Therapeutic Class Overview
Benzoyl Peroxide/Antibiotic Combinations

Therapeutic Class Overview/Summary:
This review will focus on the benzoyl peroxide/antibiotic combination products, which are approved for the topical treatment of acne vulgaris in patients 12 years of age and older.[1-6] Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules.[7-10] Four primary pathogenic factors interact in a complex manner to produce the different acne lesions. These four factors include sebum production by the sebaceous gland, *Propionibacterium acnes (P acnes)* follicular colonization, alteration in the keratinization process, and the release of inflammatory mediators to the skin.[7-10] Clindamycin phosphate and erythromycin are antibiotics that inhibit bacterial protein synthesis via interference at the bacterial ribosome. Benzoyl peroxide also exhibits antimicrobial effects against *P acnes*; however, it acts via release of free-radical oxygen species which oxidize bacterial proteins. In addition, benzoyl peroxide also demonstrates keratolytic activity, which produces drying and desquamative actions that contribute to its efficacy in comedone treatment.[11,12]

Several treatment options exist including topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, laser and light therapies, miscellaneous therapies, complementary/alternative therapies, and dietary restrictions.[7] Traditionally, the treatment of acne vulgaris was directed toward controlling *P acnes* and centered on the use of antibiotics. However, with the knowledge of the interplay between the four different pathogenic factors, acne vulgaris treatment is now directed toward as many pathogenic factors as possible. Combination treatment has the ability to target multiple pathogenic factors, including inflammatory and noninflammatory lesions.[9] Data has shown that these agents result in faster and more complete clearing of acne vulgaris lesions compared with monotherapy.[9]

There are currently two antibiotics FDA-approved in combination with benzoyl peroxide, clindamycin phosphate and erythromycin. While both combinations are formulated as a gel, there are differences in concentrations between products.

Table 1. Current Medications Available in the Therapeutic Class[1-6]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Benzoyl peroxide/clindamycin phosphate (Benzamycin Pak®, Benzamycin®*)	Acne vulgaris (adults and pediatric patients ≥12 years of age)	Gel: 2.5%/1.2% 3.75%/1.2% 5%/1% 5%/1.2%	a
Benzoyl peroxide/erythromycin (Acanya®, BenzaClin®*, Duac®, Neuac®†, Onexton®)	Acne vulgaris (adults and pediatric patients ≥12 years of age)	Gel: 5%/3% Gel Pack: 5%/3%	a

*Generic available in at least one dosage form or strength.
†Branded-generic

Evidence-based Medicine
- The safety and efficacy of benzoyl peroxide/antibiotic combinations with clindamycin phosphate or erythromycin have been evaluated in a number of clinical trials.[7-10,13-19]
- Overall, current evidence suggests that benzoyl peroxide/clindamycin phosphate and benzoyl peroxide/erythromycin are more effective than placebo and also more effective than each individual agent alone.[1-6,13-19]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Treatment recommendations vary based upon the severity and type of acne being treated. Topical treatments are the standard of care for acne treatment.[7-10]
    - Generally, topical retinoids are the first choice treatment for most types and severities of acne (or part of the recommended regimen). Other non-retinoid topical agents include: azelaic acid, benzoyl peroxide, clindamycin phosphate, and erythromycin. Bacterial resistance is a concern when treating with systemic and topical antibiotics; therefore monotherapy is discouraged.
    - Pairing an antibiotic with benzoyl peroxide is an effective option that targets *P acnes* while minimizing the development of bacterial resistance.
  - Current guidelines strongly recommend adding benzoyl peroxide to retinoids when long-term antimicrobial use is necessary due to its efficient bactericidal properties.[7-9]
    - Overall, topical benzoyl peroxide/antibiotic combination products are indicated in patients with mild to moderate acne vulgaris.[7-9]
- Other Key Facts:
  - Benzoyl peroxide/clindamycin phosphate (BenzaClin®) and benzoyl peroxide/erythromycin (Benzamycin®) must be reconstituted prior to use, while other products are premixed.[1-6]
  - There is at least one generic formulation for each combination currently available.

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Therapeutic Class Review
Benzoyl Peroxide/Antibiotic Combinations

Overview/Summary

This review will focus on the benzoyl peroxide/antibiotic combination products, which are approved for the topical treatment of acne vulgaris in patients 12 years of age and older.[1-6] Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules.[7-10] Four primary pathogenic factors interact in a complex manner to produce the different acne lesions. These four factors include sebum production by the sebaceous gland, *Propionibacterium acnes (P acnes)* follicular colonization, alteration in the keratinization process, and the release of inflammatory mediators to the skin.[7-10] Clindamycin phosphate and erythromycin are antibiotics that inhibit bacterial protein synthesis via interference at the bacterial ribosome. Benzoyl peroxide also exhibits antimicrobial effects against *P acnes*; however, it acts via release of free-radical oxygen species which oxidize bacterial proteins. In addition, benzoyl peroxide also demonstrates keratolytic activity, which produces drying and desquamative actions that contribute to its efficacy in comedone treatment.[11,12]

Several treatment options exist including topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, laser and light therapies, miscellaneous therapies, complementary/alternative therapies, and dietary restrictions.[7] Traditionally, the treatment of acne vulgaris was directed toward controlling *P acnes* and centered on the use of antibiotics. However, with the knowledge of the interplay between the four different pathogenic factors, acne vulgaris treatment is now directed toward as many pathogenic factors as possible. Combination treatment has the ability to target multiple pathogenic factors, including inflammatory and noninflammatory lesions.[9] Data has shown that these agents result in faster and more complete clearing of acne vulgaris lesions compared with monotherapy.[9]

Treatment recommendations vary based upon the severity and type of acne being treated. Topical treatments are the standard of care for acne treatment.[7-10] Generally, topical retinoids are the first choice treatment for most types and severities of acne (or part of the recommended regimen). Other non-retinoid topical agents include: azelaic acid, benzoyl peroxide, clindamycin phosphate, and erythromycin. Bacterial resistance is a concern when treating with systemic and topical antibiotics; therefore monotherapy is discouraged. However pairing an antibiotic with benzoyl peroxide is an effective option that targets *P acnes* while minimizing the development of bacterial resistance. Current guidelines strongly recommend adding benzoyl peroxide to retinoids when long-term antimicrobial use is necessary due to its efficient bactericidal properties. Overall, topical benzoyl peroxide/antibiotic combination products are indicated in patients with mild to moderate acne vulgaris.[7-9]

There are currently two antibiotics FDA-approved in combination with benzoyl peroxide, clindamycin phosphate and erythromycin. While both combinations are formulated as a gel, there are differences in concentrations between products. Benzoyl peroxide/erythromycin (Benzamycin®, Benzamycin Pak®) gel is available in a single concentration, 5%/3%. Benzoyl peroxide/clindamycin phosphate is available in several different concentrations which include 1%/5% (BenzaClin®), 1.2%/2.5% (Acanya®), 1.2%/3.75% (Onexton), and 1.2%/5% (Duac®). Benzoyl peroxide/clindamycin phosphate (BenzaClin®) and benzoyl peroxide/erythromycin (Benzamycin®) must be reconstituted prior to use, while other products are premixed. Benzoyl peroxide/antibiotic combinations should be stored in the refrigerator prior to dispensing and, with the exception of Benzamycin®, may be stored at room temperature after dispensing. Depending on the product, and expiration date of 60 to 90 days should be used after the package is opened.[1-6]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Benzoyl peroxide/clindamycin phosphate (Benzamycin Pak®, Benzamycin®*)	Topical antiinfective	a
Benzoyl peroxide/erythromycin (Acanya®, BenzaClin®*, Duac®, Neuac®†, Onexton®)	Topical antiinfective	a

*Generic available in at least one dosage form or strength
†Branded-generic

Indications

The benzoyl peroxide/antibiotic combination products are FDA-approved for the topical treatment of acne vulgaris in patients 12 years of age and older.[1-6]

There is some evidence supporting the use of benzoyl peroxide/clindamycin phosphate for the off-label use of acne rosacea.[11]

Pharmacokinetics

Table 2. Pharmacokinetics[1-6,12]

Generic Name	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Benzoyl peroxide/ clindamycin phosphate	<2/ <1 to 5	As benzoate in the urine (% not available)/ not reported	Benzoic acid/ not reported	Not reported
Benzoyl peroxide/ erythromycin	<2/ not reported	As benzoate in the urine (% not available)/ not reported	Benzoic acid/ not reported	Not reported

Clinical Trials

The safety and efficacy of benzoyl peroxide/antibiotic combinations with clindamycin phosphate or erythromycin have been evaluated in a number of clinical trials.[7-10,13-19] Overall, current evidence suggests that benzoyl peroxide/clindamycin phosphate and benzoyl peroxide/erythromycin are more effective than placebo and also more effective than each individual agent alone.[1-6,13-19]

Table 3 Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Thibout et al[13] Benzoyl peroxide/ erythromycin 5%/3% Pak applied twice daily (BPE Pak) vs vehicle Pak applied twice daily (VC Pak) vs benzoyl peroxide/ erythromycin 5%/3% jar applied twice daily (BPE jar) vs vehicle jar applied twice daily (VC jar)	DB, MC, PG, RCT Patients ≥12 years of age with 15 to80 facial lesions, 20 to 140 comedones, ≤2 nodules or cysts >5 mm and a minimum PGAS score of 1.5	N=327 8 weeks	Primary: Lesion counts (total, inflammatory [papules or pustules], noninflammatory [comedones]) Secondary: PGAS, facial-oiliness scores, global improvement and treatment acceptability by patients	Primary: Treatment with BPE Pak resulted in significant reductions in mean absolute reductions in total, inflammatory and noninflammatory lesions as compared to VC Pak (P≤0.001). Significantly more patients in the BPE Pak group achieved treatment success compared to patients in the VC Pak group (P value not reported). Absolute and proportional reductions in total lesions were similar between patients treated with BPE Pak and BPE jar. Absolute and proportional reductions in inflammatory lesions were similar between patients treated with BPE Pak and BPE jar. Proportional reductions in noninflammatory lesions were similar between patients treated with BPE Pak and BPE jar. Rates of patients achieving treatment success were similar between treatment with BPE Pak and BPE Jar (P values not reported). Secondary: Treatment with BPE Pak resulted in significantly greater improvement on all secondary variables as compared to treatment with VC Pak (PGAS; P≤0.002, facial oiliness scores; P≤0.035, patient's global improvement scores; P<0.001). Evaluation of secondary variable showed that treatment with BPE Pak and BPE Jar resulted in similar results (P value not reported).
Thiboutot et al[14] Benzoyl peroxide/ clindamycin2.0%/1.2% gel applied once daily vs	DB, MC, PG, RCT Male and female patients ≥12 years of age with moderate to	N=2,813 12 weeks	Primary: Absolute change in inflammatory and noninflammatory lesion counts from baseline to	Primary: At week 12, the benzoyl peroxide/clindamycin group had a significantly greater decrease (14.2) in inflammatory lesions compared to the other treatment groups (P<0.001). At week 12, the benzoyl peroxide/clindamycin group had a significantly greater decrease (20.5) in noninflammatory lesions compared to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clindamycin 1.2% gel applied once daily vs benzoyl peroxide 2.5% gel applied once daily vs vehicle gel applied once daily	severe acne vulgaris (score of 3 or 4 on the EGSS), with 17 to 40 inflammatory lesions, 20 to 100 noninflammatory lesions and two nodules or less		week 12, percent of patients with at least a 2-grade improvement on the EGSS (treatment success) Secondary: Percent change in inflammatory and noninflammatory lesion counts, absolute and percent change in total lesion counts, frequency of adverse events	other treatment groups (P<0.001). At week 12, 35.0% of patients treated with benzoyl peroxide/clindamycin had at least a 2-grade improvement in EGSS which was significantly more than those treated with clindamycin alone (26.0%), benzoyl peroxide alone (26.0%) or vehicle gel (-17.0%) (P<0.001). Secondary: At week 12, the benzoyl peroxide/clindamycin group had a significantly greater decrease in percent reduction (54.6%) in inflammatory lesions compared to the other treatment groups (P<0.001). Clindamycin, benzoyl peroxide and vehicle gel resulted in 46.2%, 47.5% and 29.0% reductions in inflammatory lesion counts respectively. At week 12, the benzoyl peroxide/clindamycin group had a significantly greater decrease in mean percent reduction (43.2%) in noninflammatory lesions compared to the other treatment groups (P<0.001). Clindamycin, benzoyl peroxide and vehicle gel resulted in 36.2%, 37.4% and 24.0% reductions in noninflammatory lesions respectively. Overall adverse events were reported in 5.9% of the benzoyl peroxide/ clindamycin group, 4.3% of the clindamycin group, 5.9% of the benzoyl peroxide group and 6.1% of the vehicle group. Overall, >97.0% of adverse events reported were considered mild to moderate in severity.
Webster et al[15] Benzoyl peroxide/ clindamycin 2.0%/1.2% gel applied once daily vs clindamycin 1.2% gel	DB, MC, PG, RCT Male and female patients ≥12 years of age with moderate to severe acne vulgaris (score of	N=2,813 (2,282 with moderate acne and 531 with severe acne) 12 weeks	Primary: Absolute change in the number of inflammatory and noninflammatory lesion counts from baseline to week 12, percent	Primary: At week 12, in patients with moderate acne, the median number of inflammatory and noninflammatory lesions decreased significantly more in patients treated with benzoyl peroxide/clindamycin (68.0% and 50.0%, respectively) than those treated with clindamycin (55.6% and 41.3%, respectively; P<0.001, P=0.001), benzoyl peroxide (57.7% and 43.6%, respectively; P<0.001, P=0.001) and vehicle (36.4% and 25.0%, respectively; P<0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied once daily vs benzoyl peroxide 2.5% gel applied once daily vs vehicle gel applied once daily	3 or 4 on the EGSS), with 17 to 40 inflammatory lesions, 20 to 100 noninflammatory lesions and two nodules or less		of patients with at least a 2-grade improvement on the EGSS (treatment success) Secondary: Absolute change in total lesion counts	At week 12, in patients with severe acne, the median number of inflammatory and noninflammatory lesions decreased significantly more in patients treated with benzoyl peroxide/clindamycin (48.7% and 45.1%, respectively) than those treated with vehicle (23.9% and 26.6%, respectively) (P<0.001 for both). At week 12, 32.3% of patients with moderate acne who were treated with benzoyl peroxide/clindamycin had at least a 2-grade improvement in EGSS, which was significantly greater than those treated with clindamycin (24.3%), benzoyl peroxide (23.5%) and vehicle (14.7%) (P=0.001, P<0.001, P<0.001). At week 12, 32.3% of patients with severe acne who were treated with benzoyl peroxide/clindamycin had at least a 2-grade improvement in EGSS, which was significantly greater than those treated with clindamycin (34.6%), and vehicle (23.7%) (P=0.040, P=0.001). Secondary: At week 12, in patients with moderate acne, there was a 54.1% median reduction in total lesion counts in patients treated with benzoyl peroxide/ clindamycin, which was significantly greater than those treated with clindamycin, (45.2%; P<0.001), benzoyl peroxide (47.1%; P<0.001), and vehicle (29.7%; P<0.001). At week 12, in patients with severe acne, there was a 44.4% median reduction in total lesion counts in patients treated with clindamycin/benzoyl peroxide, which was significantly greater than those treated with vehicle (19.4%; P<0.001).
Lookingbill et al[16] Benzoyl peroxide/ clindamycin 5%/1% gel applied once daily vs	AC, DB, MC, PC, PG, VC Patients 13 to 30 years of age with a minimum of 12 inflammatory	N=393 11 weeks	Primary: Lesion counts (inflammatory and non-inflammatory), global improvement (0	Primary: For weeks 2 to 11, significantly greater average percent reductions in inflammatory lesions were seen in patients treated with benzoyl peroxide/ clindamycin, clindamycin, and benzoyl peroxide as compared to those treated with vehicle gel (P≤0.002 for all compared to vehicle). Treatment with benzoyl peroxide/clindamycin resulted in significantly greater average percent reductions than either individual agent

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clindamycin 1% gel vs benzoyl peroxide 5% gel vs vehicle gel	lesions (papules and pustules) and 12 noninflammatory lesions (open and closed comedones) and ≤3 nodulocystic lesions		to 4 scale) Secondary: Safety (adverse events and tolerance scores)	(P<0.02). Results comparing clindamycin to benzoyl peroxide were similar. Significantly greater average percent reductions in noninflammatory lesions were seen in all treatment groups as compared to vehicle, beginning at week 2 for benzoyl peroxide/clindamycin, week 5 for benzoyl peroxide and week 11 for clindamycin (P≤0.004, P≤0.005, P=0.04 respectively). Treatment with benzoyl peroxide/clindamycin and benzoyl peroxide resulted in significantly greater reductions as compared to treatment clindamycin (P≤0.01); however they were not significantly different from each other. Significantly more patients treated with benzoyl peroxide/clindamycin, clindamycin, and benzoyl peroxide achieved good or excellent responses on the global improvement scale as compared to those treated with vehicle gel (P≤0.001 for each to vehicle). Treatment with benzoyl peroxide/clindamycin resulted in significantly greater improvement than either individual agent (P≤0.001). Secondary: No significant differences were found between the treatments in terms of local irritant effects. Treatment with benzoyl peroxide/clindamycin and benzoyl peroxide resulted in significantly more peeling than clindamycin (P<0.02).
Chalker et al[17] Benzoyl peroxide/ erythromycin 5%/3% gel vs benzoyl peroxide 5% gel vs	DB, RCT Patients with acne vulgaris	N=165 10 weeks	Primary: Lesion counts Secondary: Not reported	Primary: Benzoyl peroxide and erythromycin treatments were more effective than vehicle treatment. Combination benzoyl peroxide/erythromycin was more effective than either single agent. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
erythromycin 3% gel vs gel vehicle				
Cunliffe et al[18] Benzoyl peroxide/ clindamycin 5%/1% gel applied twice daily vs clindamycin 1% gel applied twice daily	DB, PG, RCT, SB Patients 13 to 30 years of age with mild to moderate acne, 15 to 100 comedones, 15 to 100 inflammatory lesions, ≤2 nodules/cysts on the face and *P acnes* counts ≥10^4 colony-forming units/square centimeter of skin	N=790 16 weeks	Primary: Percent change in lesion counts (total, inflammatory and comedones), physician's CGI score Secondary; Antimicrobial assessment (counts of total and clindamycin-resistant *P acnes* and coag-neg *S aureus),* patient CGI score, tolerability; association between bacterial counts and efficacy (post-hoc)	Primary: Both treatments resulted in significant reductions from baseline in total lesion counts, number of inflammatory lesions and number of comedones. The use of benzoyl peroxide/clindamycin resulted in significantly greater reductions in median total lesion counts compared to clindamycin (P=0.013). The median percent reductions in inflammatory lesions and comedones from baseline were significantly greater in the combination group as compared to the monotherapy group (P=0.014, P=0.018 respectively). Average physician CGI scores were significantly greater in the combination group as compared to the monotherapy group at week 16 (P=0.041). Secondary: Benzoyl peroxide/clindamycin resulted in significantly better antimicrobial efficacy than clindamycin at week 16 (P≤0.004). The use of benzoyl peroxide/clindamycin resulted in significantly fewer resistant P acnes counts (P=0.018). The use of benzoyl peroxide/clindamycin resulted in significantly fewer resistant coag-neg S aureus counts (P≤0.003). There were no significant differences between combination and monotherapy treatment in patient CGI scores or treatment acceptability scores.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Significant associates were observed between percent change from baseline in total lesion counts and comedone counts with a change in baseline in total *P acnes* counts (P<0.001 for both).
Leyden et al[19] Benzoyl peroxide/ clindamycin 5%/1% applied twice daily vs benzoyl peroxide 5% applied twice daily vs benzoyl peroxide/ erythromycin 5%/3% applied twice daily	MC, PG, RCT, SB Patients 13 to 30 years of age, with moderate to moderately severe acne, with 10 to 80 inflammatory lesions (papules and pustules) and 10 to 100 comedones in the facial area	N=492 10 weeks	Primary: Reduction from baseline in the number of inflammatory lesions, physician evaluation of overall improvement as percent change from baseline, patient assessment of efficacy and adverse events Secondary: Not reported	Primary: All treatments resulted in a decrease in average number of inflammatory lesions. The average decrease in the number of inflammatory lesions decreased significantly greater in those treated with benzoyl peroxide/clindamycin than with those treated with benzoyl peroxide (P=0.04). The average decrease in the number of inflammatory lesions was similar in patients treated with benzoyl peroxide/clindamycin and benzoyl peroxide/erythromycin (P=0.40). Physician assessment indicated improvement with all treatments. At week 10, physician assessment of improvement was significantly greater for those treated with benzoyl peroxide/clindamycin than those treated with benzoyl peroxide (P=0.04) but similar to those treated with benzoyl peroxide/ erythromycin (P value not reported). Patient assessment at week 10 indicated that benzoyl peroxide/clindamycin resulted in significantly greater improvement than treatment with benzoyl peroxide (P<0.001) but was similar to treatment with erythromycin/benzoyl peroxide (P value not reported). Dry skin was the most frequently reported adverse event and was reported at a similar rate across the groups: benzoyl peroxide/clindamycin, 4.8%; benzoyl peroxide/erythromycin, 4.3%; and benzoyl peroxide, 7.3% (P values not reported). Secondary: Not reported

Study abbreviations: DB=double-blind, MC=multicenter, PG=parallel-group, RCT=randomized control trial, SB=single=blind VC=vehicle control
Other abbreviations: CGI=clinical global impression, EGSS=evaluator's global severity score

Special Populations

Table 4. Special Populations[1-6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Benzoyl peroxide/ clindamycin phosphate	Safety and efficacy in elderly patients not reported. FDA-approved for use in children 12 years of age and older.	Not reported	Not reported	C	Unknown; use with caution.
Benzoyl peroxide/ erythromycin	Safety and efficacy in elderly patients not reported. FDA-approved for use in children 12 years of age and older.	Not reported	Not reported	C	Unknown; use with caution.

FDA=Food and Drug Administration

Adverse Drug Events

Table 5. Adverse Drug Events[1-6,12]

Adverse Event(s)	Combination Products	
	Benzoyl peroxide/ clindamycin phosphate (%)	Benzoyl peroxide/ erythromycin (%)
Application site reaction	3	0.8 to 2.5
Blepharitis	-	<2
Burning	<1 to 5	0.8 to 2.5
Dry skin/dryness	1 to 15	5.0 to 7.6
Edema	-	a
Erythema	5 to 26	0.8 to 2.5
Inflammation	-	a
Irritation	-	a
Itching	-	a
Oily skin/oiliness	-	a
Peeling	2 to 17	<1
Photosensitivity	-	<2
Pruritus	2 to 15	<2
Skin discoloration	-	a
Stinging	-	0.8 to 2.5
Sun burn	1	-
Tenderness	-	a

- Event not reported
a % not specified.

Contraindications

Table 6. Contraindications[1-6]

Contraindication	Benzoyl peroxide/ clindamycin phosphate	Benzoyl peroxide/ erythromycin
History of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.	a	
Hypersensitivity to lincomycin.	a	
Hypersensitivity to the active drugs or any of its components.	a	a

Warnings/Precautions

Table 7. Warnings and Precautions[1-6,12]

Warnings/Precaution	Benzoyl peroxide/ clindamycin phosphate	Benzoyl peroxide/ erythromycin
Concomitant use with erythromycin products: avoid concurrent use	a	
Concomitant use with other topical acne therapies: use caution: peeling, desquamating, or abrasive products, as cumulative irritation may occur	a	a
Dermatologic: natural or artificial sunlight (e.g., tanning beds, sun lamps) should be avoided	a	
Gastrointestinal: bloody diarrhea and colitis (including pseudomembranous colitis) have been reported; discontinue use if significant diarrhea occurs	a	a
Immunologic : anaphylaxis and other severe allergic reactions have been reported	a	
Severe irritation may occur; discontinuation of therapy may be necessary		a
Topical use only; avoid contact with eyes and all mucous membranes	a	a

Drug Interactions

Table 8. Drug Interactions[1-6,12]

Generic Name	Interacting Medication or Disease	Potential Result
Benzoyl peroxide/ clindamycin phosphate	Erythromycin products	Concurrent use of clindamycin and erythromycin may result in antagonistic antimicrobial effects.
Benzoyl peroxide/ erythromycin	Clindamycin products	Concurrent use of erythromycin and clindamycin may result in antagonistic antimicrobial effects.
Benzoyl peroxide/ erythromycin	Warfarin	Concurrent use of erythromycin and warfarin may result in an increased risk of bleeding.

Dosage and Administration

Benzoyl peroxide/clindamycin phosphate (BenzaClin®) and Benzoyl peroxide/erythromycin (Benzamycin®) must be reconstituted prior to dispensing. For BenzaClin®, clindamycin phosphate powder is dissolved using purified water. The resulting solution is stirred into the gel until homogenous in appearance (one to two minutes). For Benzamycin®, the same procedure is followed except erythromycin powder is dissolved using 70% ethyl alcohol. All products can be stored at room temperature after dispensing except for Benzamycin®, which has to remain refrigerated.[1-6]

Table 9. Dosing and Administration[1-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Benzoyl peroxide/ clindamycin phosphate	Acne vulgaris: Gel (BenzaClin®): Apply twice daily to affected areas, morning and evening, use on washed and dried skin Gel (Acanya®, Duac®, Onexton®): Apply once daily to affected areas, use on washed and dried skin	Acne vulgaris: Refer to adult dosing. Safety and efficacy in patients under the age of 12 have not been established.	Gel: 2.5%/1.2% 3.75%/1.2% 5%/1% 5%/1.2%
Benzoyl peroxide/ erythromycin	Acne vulgaris: Gel: Apply twice daily to affected areas, morning and evening, use on washed and dried skin	Acne vulgaris: Refer to adult dosing. Safety and efficacy in patients under the age of 12 have not been established.	Gel: 5%/3% Gel Pack: 5%/3%

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
European Academy of Dermatology and Venereology: **European Evidence-based (S3) Guidelines for the Treatment of Acne (2012)**[8]	Treatment of Comedonal Acne · Recommended: o Adapalene · Considerations: o BPO, azelaic acid · Not recommended: o Topical antibiotics o Hormonal antiandrogens, systemic antibiotics and/or systemic isotretinoin o Artificial UV radiation Treatment of Mild-to-Moderate Papulopustular Acne · Strong recommendation: o The fixed-dose combination adapalene and BPO o The fixed-dose combination clindamycin and BPO · Recommended: o Azelaic acid, BPO, topical retinoids (adapalene) o Combination of a systemic antibiotic with adapalene (in case of more widespread disease) · Considerations: o Blue light monotherapy o The fixed-dose combination of erythromycin and tretinoin o The fixed-dose combination of isotretinoin and erythromycin o Oral zinc o Combination of a systemic antibiotic with either BPO or with adapalene in fixed combination with BPO (in case of more widespread disease) · Not recommended: o Topical antibiotics as monotherapy

Clinical Guideline	Recommendations
	o Treatment with artificial UV radiation o The fixed-dose combination of erythromycin and zinc o Systemic therapy with anti-androgens, antibiotics, and/or isotretinoin <u>Treatment of Severe Papulopustular Acne</u> · Strong recommendation: o Oral isotretinoin monotherapy · Recommended: o Systemic antibiotics in combination with adapalene, with the fixed-dose combination of adapalene/BPO or in combination with azelaic acid · Considerations: o Oral anti-androgens in combination with oral antibiotics o Oral anti-androgens in combination with topical treatment o Systemic antibiotics in combination with BPO · Not recommended: o Single or combined topical monotherapy o Oral antibiotics as monotherapy o Oral anti-androgens as monotherapy o Visible light as monotherapy o Artificial UV radiation sources <u>Treatment of Nodular/Conglobate Acne</u> · Strong recommendation: o Oral isotretinoin · Recommended: o Systemic antibiotics in combination with azelaic acid · Considerations: o Oral anti-androgens in combination with oral antibiotics o Systemic antibiotics in combination with adapalene, BPO or the adapalene-BPO fixed-dose combination · Not recommended: o Topical monotherapy o Oral antibiotics as monotherapy o Oral anti-androgens as monotherapy o Artificial UV radiation sources o Visible light as monotherapy
American Academy of Dermatology: **New Insights into the Management of Acne: An Update from the Global Alliance to Improve Outcomes in Acne Group (2009)**[9]	· Acne vulgaris should be managed early and aggressively as a chronic disease to limit scarring; the disease is self-limiting in only 60% of cases. · Oral isotretinoin, the most effective acne vulgaris treatment developed to date, is administered during a 20 week period and sometimes must be given in repeated courses. · The combination of a topical retinoid and antimicrobial agent remains the preferred treatment approach for the majority of patients with acne vulgaris, especially in the presence of inflammatory lesions. · Due to the risk of bacterial resistance, antibiotics should be used for the shortest duration and should not be used as monotherapy but in combination with benzoyl peroxide. · Topical antibiotics combined with benzoyl peroxide and a topical retinoid may be used in mild to moderate acne vulgaris; oral antibiotics are recommended for moderate to moderately severe acne vulgaris. · Topical retinoids alone or in combination with benzoyl peroxide is recommended for the maintenance of acne vulgaris.

Clinical Guideline	Recommendations
	· Long term antibiotic use may be required in the rare cases in which the patient experiences acne vulgaris flares when oral antibiotics are discontinued. Global alliance acne vulgaris treatment algorithm · For mild acne vulgaris (comedonal), treatment with a topical retinoid is considered first line; treatment with an alternative topical retinoid or azelaic acid or salicylic acid are considered alternatives. · For mild acne vulgaris (mixed and papular/pustular), treatment with a topical retinoid and a topical antimicrobial is considered first line; treatment with alternative topical retinoid and alternative topical antimicrobial, or azelaic acid are considered alternatives. · For moderate acne vulgaris (mixed and papular/pustular), treatment with oral antibiotic and a topical retinoid with or without benzoyl peroxide is considered first line; treatment with an alternative oral antibiotic and alternative topical retinoid with or without benzoyl peroxide are considered alternatives. · For moderate acne vulgaris vulgaris (nodular), treatment with an oral antibiotic and a topical retinoid and benzoyl peroxide is considered first line; treatment with oral isotretinoin or alternate oral antibiotic and an alternate topical retinoid (with or without) benzoyl peroxide/azelaic acid are considered alternatives. · For severe acne (nodular/conglobate), treatment with oral isotretinoin is considered first line; treatment with high dose oral antibiotic and a topical retinoid and benzoyl peroxide are considered alternative. · For maintenance therapy (mild to severe acne vulgaris), treatment with a topical retinoid with or without benzoyl peroxide is considered first line.
American Academy of Dermatology: **Guidelines of Care for Acne Vulgaris Management (2007)**[10]	Standard of care · Topical therapy is the standard of care in acne vulgaris treatment. · Systemic antibiotics are used in moderate to severe acne vulgaris and treatment-resistant forms of inflammatory acne vulgaris. · Intralesional corticosteroid injections are effective for large inflammatory lesions. Topical therapy · Topical retinoids reduce obstruction within the follicle and are useful in the management of both comedonal and inflammatory acne vulgaris. · The relative efficacy between topical retinoids (i.e. tretinoin, adapalene, tazarotene, isotretinoin [not available topically in the United States]) is unclear. · Benzoyl peroxide is a bactericidal agent with the ability to prevent or eliminate the development of *P acnes* resistance, and is therefore used in combination with oral or topical antibiotics. · Topical antibiotics (erythromycin and clindamycin) are effective in the treatment of acne vulgaris but are more effective when used in combination with benzoyl peroxide due to a synergy as well as the resulting elimination or reduction of bacterial resistance. · Salicylic acid has moderately effective and less potent comedolytic properties than topical retinoids and is therefore used in patients intolerant to dermatological effects caused by topical retinoids. · Azelaic acid has shown to be effective, with comedolytic and antibacterial properties. · The role of aluminum chloride, resorcinol, sodium sulfacetamide, sulfur and

Clinical Guideline	Recommendations
	zinc in the management of acne vulgaris is unclear due to limited clinical evidence and/or peer-reviewed literature. Systemic antibiotics · Doxycycline and minocycline are more effective than tetracycline. · Minocycline has been shown to be superior to doxycycline in reducing *P acnes*. · Erythromycin is effective but associated with bacterial resistance and therefore its use should be limited to those who cannot tolerate tetracyclines (i.e. pregnant women and children <8 years old due to the potential damage to the skeleton or teeth). Hormonal agents · Oral contraceptives containing norgestimate with ethinyl estradiol and norethindrone acetate with ethinyl estradiol are Food and Drug Administration (FDA) approved for the management of acne vulgaris. Isotretinoin · Isotretinoin, a vitamin A derivative, is approved for the treatment of severe recalcitrant nodular acne vulgaris and possibly effective in treatment-resistant acne vulgaris or acne vulgaris producing physical or psychological scarring. · Since isotretinoin is a potent teratogenic, females of child-bearing age must only be treated if they are participating in the approved pregnancy prevention and management program (iPLEDGE).

BPO=benzoyl peroxide, NIL=non-inflammatory lesions, UV=ultraviolet

Conclusions

There are currently two antibiotics FDA-approved in combination with benzoyl peroxide, clindamycin phosphate and erythromycin.[1-6] Benzoyl peroxide/clindamycin phosphate (BenzaClin®, Acanya®, Onexton®, Duac®) and benzoyl peroxide/erythromycin (Benzamycin®, Benzamycin Pak®) are all formulated as a gel. Different products are formulated in different concentrations and several products require reconstitution prior to dispensing (BenzaClin®, Benzamycin®).[1-6] Topical retinoids alone or in combination with other topical treatments (e.g., benzoyl peroxide) are usually recommended first line for the treatment of acne. However, depending on the type and severity of the acne, other regimens may be recommended. Overall, topical benzoyl peroxide/antibiotic combination products are indicated in patients with mild to moderate acne vulgaris. Pairing an antibiotic with benzoyl peroxide is an effective option that targets *P acnes* while minimizing the development of bacterial resistance. [7-10] Clinical trials that evaluated benzoyl peroxide/clindamycin phosphate and benzoyl peroxide/erythromycin have shown that each is more effective than placebo and also more effective than each individual agent alone.[1-6,13-19]

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