



Acne Agents, Topical Therapeutic Class Review (TCR)

January 10, 2022

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FDA-APPROVED INDICATIONS

All products included in this review are indicated for the topical treatment of acne vulgaris. Tazarotene (Tazorac) is additionally indicated for the treatment of plaque psoriasis. Sodium sulfacetamide/sulfur (Avar, Avar E, Avar E-LS, Avar LS, BP 10-1, BP Cleansing Wash, Plexion, SSS 10-5, SulfaCleanse, Sumadan, Sumaxin) is additionally indicated for topical control of acne rosacea and seborrheic dermatitis. Sodium sulfacetamide (Ovace, Ovace Plus, Ovace Plus Wash) is indicated for seborrheic dermatitis and seborrhea sicca, in addition to treatment of secondary bacterial infections of the skin due to organisms susceptible to sulfonamides.

Drug	Manufacturer
adapalene (Rx and OTC) (Differin®) ¹ (Effaclar Gel) ²	generic* Galderma L'oreal
adapalene/benzoyl peroxide (Epiduo® Forte) ³⁴	generic Galderma
azelaic acid (Azelex®) ⁵	Almirall
benzoyl peroxide (Rx and OTC) (Acne Medication) ⁶ (Acne Spot Treatment) ⁷ (Advanced Acne Wash) ⁸ (Benzefoam®) ⁹ (Benzepro®) ¹⁰ (BP) ¹¹ (BP Foaming Wash) ¹² (BPO) ¹³ (BP Wash) ¹⁴ (Cerave® Acne Cleanser) ¹⁵ (Daylogic™ Acne Treatment) ¹⁶ (Effaclar Duo) ¹⁷ (Enzoclear™) ¹⁸ (OC8) ¹⁹ (Panoxyl®) (Persa-Gel®) ²⁰ (Riax®) ²¹	generic Rugby CVS Elorac Bausch Prugen Cintex Acella Acella Cintex L'Oreal Rite Aid L'Oreal Lacer Ferndale GSK Consumer/Crown J&J Consumer Artesa Labs
benzoyl peroxide/clindamycin (Acanya®) ²² (BenzaClin®) ²³ (Neuac®) ²⁴ (Onexton®) ²⁵	generic* Valeant Valeant Medimetriks Valeant
benzoyl peroxide/erythromycin (Benzamycin®) ²⁶	generic Valeant
benzoyl peroxide/hydrocortisone (Vanoxide-HC) ²⁷	Summers

OTC = over-the-counter; Rx = prescription required

FDA-Approved Indications (continued)

Drug	Manufacturer
clascoterone (Winlevi®) ²⁸	Cassiopea/Sun
clindamycin (Cleocin T®) ²⁹ (Clindacin® ETZ) ³⁰ (Clindacin P®) ³¹ (Clindagel®) ³² (Evoclin®) ³³	generic* Pharmacia/Pfizer Medimetriks Medimetriks Valeant/Bausch Mylan
dapson (Aczone®)* ³⁴	generic Almirall
erythromycin (Ery) ³⁵ (Erygel®) ³⁶	generic Perrigo Mylan
minocycline (Amzeeq®) ³⁷	Vyne
salicylic acid (OTC) (Acne Treatment) ³⁸ (Advanced Acne Spot Treatment) ³⁹ (Clearasil Daily Clear) ⁴⁰ (Clearasil Prevention Wash) (Effaclar Cleanser) ⁴¹ (Oil-Free Acne Wash) ⁴² (Rapid Clear®) ⁴³	McKesson/Rite Aid CVS Reckitt L'oreal Equaline Vitamin/Neutrogena Neutrogena
salicylic acid/benzoyl peroxide (Effaclar Acne System) ⁴⁴	L'Oreal
sodium sulfacetamide (Klaron®) ⁴⁵ (Ovace®) ⁴⁶ (Ovace® Plus) ^{47,48,49} (Ovace® Plus Wash®) ⁵⁰	generic Valeant Mission Mission Mission

OTC = over-the-counter; Rx = prescription required

FDA-Approved Indications (continued)

Drug	Manufacturer
sodium sulfacetamide/sulfur (Avar®) ^{51,52} (Avar-e®) ⁵³ (Avar-e® LS) ⁵⁴ (Avar® LS) ⁵⁵ (BP 10-1) ⁵⁶ (BP Cleansing Wash) ⁵⁷ (Plexion®) ⁵⁸ (Rosula®) ⁵⁹ (SSS 10-5) ⁶⁰ (SulfaCleanse®) ⁶¹ (Sumadan®) ⁶² (Sumaxin®) ⁶³ (Sumaxin® TS) ⁶⁴	generic Mission Mission Mission Mission Acella Acella Brava/Mission Avion Acella Prugen Medimetricks Medimetricks Medimetricks
sulfur (Palmers Skin Success®) ⁶⁵ (Sulfo Lo®) ⁶⁶	E. T. Browne Crown
tazarotene (Arazlo®) ⁶⁷ (Fabior®) ⁶⁸ (Tazorac®) ^{69,70}	generic Bausch Mayne Almirall
tretinoin (Altreno®) ⁷¹ (Atralin®) ⁷² (Avita®) ⁷³ (Refissa®) ⁷⁴ (Retin-A®) ⁷⁵ (Retin-A Micro®) ⁷⁶ (Tretin-X®)	generic Valeant/Bausch Valeant Mylan Zo Skin Health Valeant Valeant Onset Dermatologics
tretinoin/benzoyl peroxide (Twyneo®) ⁷⁷	Galderma
tretinoin/clindamycin (Ziana®) ⁷⁸ (Veltin®) ⁷⁹	generic Valeant Stiefel/Aqua
triferotene (Aklief®) ⁸⁰	Galderma

OTC = over-the-counter; Rx = prescription required

* Generic versions of Differin 0.1% lotion (adapalene) and **Fabior 0.1% foam** are available only as authorized generics.

Clindacin ETZ, Clindacin P, Clindacin PAC, Ery, Neuac, Refissa, and Tretin-X are approved under abbreviated new drug applications (ANDAs) as generic products.

Products that are available as convenience kits are not included in this Therapeutic Class Review.

OVERVIEW

Acne vulgaris is the most common cutaneous condition in the United States (US).⁸¹ It is a disorder that affects primarily teenagers and young adults, but it can sometimes persist beyond young adulthood. In adolescence, sebaceous glands increase sebum release after puberty. Small cysts called comedones form in hair follicles due to blockage of the pore from accumulated sebum and keratinous material. Bacteria, most often *Propionibacterium acnes*, release free fatty acids from sebum within the comedones, which causes inflammation to form a cyst. This results in rupture of the cyst wall and subsequent inflammatory reaction due to extrusion of oily and keratinous debris from the cyst.

Classification of the severity of acne is not standardized in the published medical literature.⁸² One method of classification is to evaluate the number and type of lesions. There are 3 categories of the severity of acne and include either acne occurring on the face or the trunk of the body. These categories are graded as mild, moderate, or severe depending on the presence and number of lesions, which consist of comedones, papules, pustules, and/or cysts. Mild acne is defined by the presence of fewer than 20 comedones, fewer than 15 inflamed papules, or fewer than 30 lesions consisting of the combination comedones and papules. Moderate acne is defined by the presence of 15 to 50 papules and pustules in addition to comedones and rare cysts, and the total number of lesions on the face can range from 30 to 125. Severe acne is defined by the presence of mostly inflamed nodules and cysts and includes more than 125 lesions consisting of comedones, papules, and pustules.

The goals of treatment include resolution of lesions, scar prevention, and reduction of psychological morbidities.⁸³ This is achieved by decreasing sebaceous gland activity, bacterial population, and inflammation. The available products work by different mechanisms to attack the causative events. Typically, retinoids, such as tretinoin (Altreno, Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X), adapalene (Differin, Effaclar), tazarotene (Arazlo, Fabior, Tazorac), and trifarotene (Aklief) are used to inhibit comedone formation, while antibiotics, such as clindamycin (Cleocin T, Clindacin ETZ/P/PAC, Clindagel, Evoclin), erythromycin (Ery, Erygel), or minocycline (Amzeeq), suppresses *P. acnes*. Combination therapy is useful to limit growing resistance to antibacterial therapy, as well as enhance the efficacy of antibiotics by improving penetration into the lesions.^{84,85,86} Since 1990, prescribing has trended more toward agents not reliant on antibacterial mechanisms.⁸⁷

In May 2013, the American Acne and Rosacea Society developed the first detailed, evidence-based clinical guidelines for the management of pediatric acne including issues of special concern when treating pediatric patients.⁸⁸ The guidelines are endorsed by the American Academy of Pediatrics (AAP). The guidelines recommended topical benzoyl peroxide, a topical retinoid, or topical combination therapy that includes benzoyl peroxide plus an antibiotic, with or without a retinoid, for initial treatment of mild to moderate pediatric acne. Additional treatment considerations listed within the guidelines are oral antibiotics, hormonal therapy, and isotretinoin. The treatment algorithms include therapy for adolescent, pre-adolescent, infantile, and neonatal acne and consider psychosocial effects on acne, adherence to treatment, and the effects of diet on acne.

The May 2016 American Academy of Dermatology (AAD) guidelines recommend benzoyl peroxide or combinations with erythromycin or clindamycin for mild acne or in conjunction with a topical retinoid or systemic antibiotic for moderate to severe acne.⁸⁹ They note that benzoyl peroxide is effective to prevent bacterial resistance, but topical erythromycin and clindamycin as monotherapy are not recommended due to resistance. Topical dapsone 5% gel is recommended for inflammatory acne, particularly in female adults, while azelaic acid is beneficial as an adjunctive treatment for patients with post inflammatory

dyspigmentation. For preadolescent acne in children, topical adapalene, tretinoin, and benzoyl peroxide are recommended. The guidelines state topical retinoids play a key role in monotherapy for comedonal acne or as combination therapy with other topical or oral antimicrobials for patients with mixed or primarily inflammatory acne lesions. The guidelines recommend combination therapy with agents with different mechanisms to target acne pathogenesis in the majority of patients. They also state that evidence of sulfur (Palmers Skin Success, Sulfo-Lo), nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc use for acne treatment is limited. The guidelines also note that emerging data suggest a link between a patients' diet and acne development. A high glycemic diet or milk intake, specifically skim milk, may lead to acne. Specific dietary changes are not recommended at this time given the limited data.

According to the 2018 update to the consensus guidelines developed by the Global Alliance to Improve Outcomes in Acne, retinoids should form the cornerstone of acne therapy. Retinoid products are generally similar in efficacy, and their efficacy improves with higher concentrations.⁹⁰ Early treatment with retinoids can minimize the risk of post inflammatory hyperpigmentation (PIH), by inhibiting tyrosinase and by blocking pigment transfer from melanocytes to keratinocytes. Topical retinoid monotherapy may be sufficient in some cases. Benzoyl peroxide or an oral antibiotic may be added as needed. For most patients with inflammatory acne, comedonal acne, or both, a topical retinoid plus benzoyl peroxide is first-line therapy. Topical antibiotics should not be used as monotherapy due to rapid development of resistance; benzoyl peroxide is a potent bactericidal agent and is the preferred topical antimicrobial to support good antimicrobial stewardship. Topical retinoids, with or without benzoyl peroxide, are the treatment choice for maintenance therapy. Studies have shown that maintenance therapy with a topical retinoid achieved sustained reductions in microcomedones, resulting in fewer active acne lesions. Efficacy in maintenance therapy has also been demonstrated for adapalene, adapalene/benzoyl peroxide, tazarotene, and azelaic acid.

Benzoyl peroxide has bactericidal, keratolytic, and comedolytic activity and has been useful as a single agent and in combination with antibiotics or retinoids in decreasing the number of lesions in mild to moderate acne.⁹¹ Combining a topical antibiotic with benzoyl peroxide increases efficacy, is less irritating, and reduces the development of resistant strains of *P. acnes*.^{92,93,94,95} There are many different strengths and formulations available for benzoyl peroxide. It is unknown if there is increased efficacy from higher or lower concentrations of the products, but the incidence of adverse effects may increase with greater concentration of drug.

Clindamycin has been associated with greater incidences of adverse effects when introduced into the systemic circulation compared to erythromycin, but the topical application of these products allows for minimal systemic absorption. There does not appear to be any significant differences in the efficacy of these topical antibiotics. As stated above, monotherapy with these topical antibiotics is not recommended due to the development of bacterial resistance.^{96,97}

Azelaic acid (Azelex) exhibits comedolytic and antibacterial properties; it is not viewed as initial therapy.⁹⁸ Investigation of clinical efficacy for sodium sulfacetamide is lacking, as are the effects of combinations with sulfur. Sulfur is an older therapeutic agent that exhibits antimicrobial and keratolytic activity and has demonstrated some usefulness in the treatment of acne.^{99,100} The clinical evidence, however, demonstrating the efficacy of sulfur in acne treatment has not been consistently or reliably proven. Dapsone (Aczone) is a topical sulfone developed from the oral formulation which is used to treat leprosy.¹⁰¹ Adapalene and tazarotene have been shown to be at least as effective as tretinoin, often with

a lower incidence of adverse effects.¹⁰² However, tazarotene gel may be more irritating than tretinoin or adapalene. The tazarotene cream, lotion, and foam formulations may be better tolerated, but how it compares in effectiveness with adapalene or tretinoin remains to be determined.

In 2016, the FDA approved Differin 0.1% gel (adapalene) for the treatment of acne without a prescription.¹⁰³ The FDA noted that usage and exposure were key review issues in evaluating the potential risks of marketing for over-the-counter (OTC) use. They state that data suggests that larger package size may lead to increased usage, while limiting package size may reduce overconsumption; package sizes exceeding 45 grams require pre-submission requirements to justify the large package size.

While systemic treatment is generally required in cases of severe acne, and hormonal therapy is available for females, this review focuses on the available topical preparations for acne treatment.

Trifarotene (Aklief) and minocycline topical foam (Amzeeq) were FDA approved in 2019 and use of these agents are not addressed in the guidelines discussed above. Clascoterone (Winlevi) was FDA approved in 2020. Thus, its use is also not addressed in these guidelines.

Data on efficacy of sulfur cleansing bar (Palmers Skin Success, Sulfo-Lo) is limited; therefore, the detail discussed will be limited to select sections of this therapeutic class review.

PHARMACOLOGY¹⁰⁴

Clindamycin and erythromycin are antibiotics that inhibit bacterial protein synthesis at the ribosomal level by binding to the 50S ribosome and affecting the process of peptide chain initiation. They have been shown to have *in vitro* activity against *P. acnes*, an organism commonly associated with acne vulgaris. Antagonism has been reported between clindamycin and erythromycin. Sulfonamides such as sodium sulfacetamide (Avar, Avar E, Avar E-LS, Avar LS, BP 10-1, BP Cleansing Wash, Klaron, Ovace, Ovace Plus, Plexion, Rosula, SSS-10-5, SulfaCleanse, Sumadan, Sumaxin) probably work by acting as a competitive inhibitor of para-aminobenzoic acid utilization (PABA). PABA is an essential component for bacterial growth. Minocycline foam (Amzeeq) is a tetracycline antibiotic. It is generally bacteriostatic against most organisms. However, tetracyclines may be bactericidal at high concentrations. Tetracyclines bind to the 30S ribosomal subunit, thus preventing protein synthesis. Due to its lipid solubility, minocycline can pass directly through the bacterial cell's lipid bilayer to exert its effect. The exact mechanism of action of minocycline foam (Amzeeq) is unknown. Although, *in vitro* study data have demonstrated activity against *P. acnes*.

Benzoyl peroxide has a keratolytic and desquamative effect that may contribute to its efficacy. Benzoyl peroxide is bactericidal with activity against *P. acnes*, which is believed to be due to its oxidizing properties. It is available in combination with other agents, such as antibiotics and sulfur, which contributes a mild keratolytic action. Salicylic acid causes desquamation of hyperkeratotic epithelium.

The exact mechanism of action of azelaic acid (Azelex) is not known. It has been shown to have antibacterial activity against *P. acnes* and *Staphylococcus epidermidis*, as well as a normalization of keratinization that leads to an anticomedonal effect.

Clascoterone (Winlevi) an androgen receptor inhibitor. The exact mechanism of action of clascoterone is unknown. However, limiting the ability of dihydrotestosterone to bind to androgen receptors, helps decrease the production of sebum production and inflammation which aides in the treatment of acne vulgaris.

The exact mechanism of action of dapsone (Aczone) in the treatment of acne vulgaris is unknown, but *in vitro* studies suggest that it may suppress neutrophil recruitment oxidation, which may help prevent the production of toxic respiratory and secretory products. It may also have antimicrobial activity.

Tazarotene (Arazlo, Tazorac, Fabior) is a retinoid prodrug that when activated, has antihyperproliferative, differentiation normalizing, and anti-inflammatory effects. The exact mechanism of action is unknown. Tretinoin (Altreno, Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X), another retinoid, works by decreasing cohesiveness of follicular epithelial cells and decreasing microcomedone formation. It may also stimulate mitotic activity and increase turnover of follicular epithelial cells, causing extrusion of the comedones.

Adapalene (Differin, Effaclar, Epiduo Forte) is a topical retinoid-like drug. It modulates cellular differentiation, keratinization, and inflammatory processes. Although the exact mechanism of action is unknown, adapalene may normalize the differentiation of follicular epithelial cells, resulting in decreased microcomedone formation.

Trifarotene (Aklief) is an agonist of retinoic acid receptors (RAR), with particular activity at the gamma subtype of RAR. Stimulation of RAR results in modulation of target genes which are associated with various processes, including cell differentiation and mediation of inflammation. However, the exact mechanism of action of trifarotene to treat acne is unknown. Topical retinoids, such as trifarotene, are known to influence proliferation and differentiation of cells, increase follicular epithelial turnover, and accelerate the shedding of corneocytes. These actions result in an expulsion of mature comedones and suppression of microcomedone formation.

PHARMACOKINETICS [105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149](#)

Less than 2% of benzoyl peroxide is absorbed in the systemic circulation. Due to the lipophilic nature, benzoyl peroxide concentrates in the lipid-rich sebaceous follicles. The small amount that is systemically absorbed is converted to benzoic acid, which is further metabolized to benzoate. Benzoate is then excreted in the urine.

Azelaic acid (Azelex) is approximately 4% bioavailable, and any absorbed drug is excreted unchanged in the urine. Its half-life is about 12 hours.

Pharmacokinetic studies with adapalene (Differin, Effaclar) and the combination product with benzoyl peroxide (Epiduo Forte) have only found trace amounts of adapalene in plasma when administered topically. Excretion is primarily by the biliary route.

Systemic concentrations of clascoterone (Winlevi) were achieved by day 5 of treatment with twice daily application. Cortexolone is the primary metabolite of clascoterone and is detectable in plasma. The exact routes of excretion and elimination for clascoterone have not been determined.

Topically-administered clindamycin has some systemic absorption and is only 1% available systemically. The low levels seen in the plasma are excreted unchanged in the urine.

The systemic exposure to dapsone 5% gel (Aczone) versus oral dapsone 100 mg was studied for 14 days. The results indicated that twice daily topical application of the agent leads to less systemic exposure to the drug than the 100 mg once daily oral administration of the drug. Patients applying the drug topically

had approximately 100-times less exposure to the active drug, as measured by the area-under-the curve (AUC), than patients taking the drug orally.

Topically-administered erythromycin is not detectable in the plasma.

In a 21-day pharmacokinetic study, steady-state was reached by day 6 and systemic accumulation of minocycline foam (Amzeeq) was not detected.

Topically administered salicylic acid results in percutaneous absorption, yet systemic exposure is negligible with normal use. Approximately 10% of applied salicylates can remain in the skin after dermal application, while acute toxicity is rarely seen.

Sulfacetamide (Klaron, Ovace, Ovace Plus, Ovace Plus Wash) is approximately 4% bioavailable and is excreted in the urine unchanged. The half-life of sulfacetamide varies between 7 and 13 hours. Absorption through intact skin has not been determined for sodium sulfacetamide (Avar, Avar E, Avar E-LS, Avar LS, BP 10-1, BP Cleansing Wash, Plexion, Rosula, SSS 10-5, SulfaCleanse, Sumadan, Sumaxin). Approximately 1% of topical sulfur is systemically absorbed.

Tazarotene (Arazlo, Tazorac, Fabior) is converted by ester hydrolysis to its active metabolite, tazarotenic acid. There is little parent compound absorbed in the plasma, and the small amount is highly plasma protein-bound. Tazarotenic acid is eliminated by the urinary and fecal routes. Tazarotene gel and cream have a half-life of about 18 hours. Tazarotene foam has a half-life of about 8 hours. The half-life of tazarotene lotion has not been reported.

Tretinoin (Altreno, Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X) has only been found in trace amounts in plasma when applied topically. It is a metabolite of vitamin A.

Systemic concentrations of trifarotene (Aklief) reached steady state following 2 weeks of treatment. The terminal half-life ranged from 2 to 9 hours, and the drug is primarily excreted by the feces. Plasma protein binding is approximately 99.9%. No drug accumulation is expected with long-term use.

CONTRAINDICATIONS/WARNINGS^{150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193}

Products containing clindamycin or erythromycin (Acanya, Benzacilin, Benzamycin, Neuac, Onexton, Cleocin T, Clindagel, Clindacin P, Clindacin PAC, Clindacin ETZ, Evoclin, Ery, Erygel, Veltin, Ziana) are contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Sulfacetamide (Avar, Avar E, Avar E-LS, Avar LS, BP Cleansing Wash, Klaron, Ovace, Ovace Plus, Ovace Plus Wash, Plexion, SSS 10-5, SulfaCleanse, Sumadan, Sumaxin) is contraindicated in patients with hypersensitivity to sulfonamides. Sodium sulfacetamide/sulfur is not to be used by patients with kidney disease. Tazarotene (Arazlo, Fabior, Tazorac) is contraindicated in pregnant women or women who may become pregnant.

Topical dapsona gel (Aczone) is contraindicated in persons with a hypersensitivity to dapsona and any other component in the formulation. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or congenital or idiopathic methemoglobinemia using dapsona gel are more susceptible to drug induced methemoglobinemia. Avoid use of dapsona gel (Aczone) in patients with congenital or idiopathic methemoglobinemia. Topical administration of dapsona gel did not demonstrate peripheral

neuropathy or skin reactions as reported with oral administration. Oral dapsone has produced dose-related hemolysis and hemolytic anemia.

Minocycline foam (Amzeeq) is contraindicated in patients with known hypersensitivity to and tetracycline or another component of the product.

Azelaic acid (Azelex) can cause hypopigmentation. Tretinoin (Altreno, Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X) may cause temporary hyper- or hypo-pigmentation.

For patients using products containing adapalene (Differin, Effaclar, Epiduo Forte), tretinoin (Altreno, Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X, Twyneo, Veltin, Ziana), trifarotene (Aklief), or benzoyl peroxide, exposure to sunlight should be limited (including sunlight and sunlamps). Use of sunscreen and protective clothing is recommended. Patients taking other photosensitizing medications should use additional caution. Weather extremes, such as wind or cold, may also be irritating. Patients should use caution to avoid contamination of hair, fabrics, and carpet with benzoyl peroxide products as bleaching and/or discoloration may result.

Erythema, scaling, dryness, and stinging/burning may be experienced with the use of adapalene/benzoyl peroxide gel (Epiduo Forte) and trifarotene (Aklief). These reactions are most likely to occur during the first 4 weeks of treatment. Reactions are generally mild to moderate in intensity and typically lessen with continued use. Application site irritation, dryness, erythema, pain, and exfoliation may also develop with use of tretinoin-containing products (Altreno, Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X, Twyneo). Depending upon severity, patients using adapalene/benzoyl peroxide gel, tretinoin or trifarotene should be advised to use a moisturizer and/or reduce the frequency of application.

Adapalene/benzoyl peroxide gel and trifarotene cream should not be applied to cuts, abrasions, eczematous, or sunburned skin. As with other retinoids, the use of 'waxing' as a depilatory method should be avoided on skin surfaces treated with adapalene/benzoyl peroxide gel.

Hypothalamic-pituitary-adrenal (HPA) suppression may occur as a result of treatment with clascoterone. This condition can be reversed after clascoterone has been discontinued. Clascoterone may cause local irritation and use with other irritating topical products should be limited. Do not apply to cuts, abrasions, eczematous or sunburned skin.

Pseudomembranous colitis has been reported with bacterial agents such as clindamycin and erythromycin, ranging in severity from mild to life-threatening, when administered orally or parenterally. Absorption of these antibiotics through the skin is minimal, however.

Clostridium difficile associated diarrhea (CDAD) has been reported with most oral antibiotics, including minocycline, and can range from mild diarrhea to fatal colitis. CDAD should be considered in all patients who present with diarrhea following antibiotic use. If CDAD is suspected, discontinue antibiotic use.

While systemic absorption of topical minocycline foam is minimal, and serious adverse reactions were not seen in clinical studies, the adverse reactions associated with oral minocycline (e.g. hepatotoxicity, renal toxicity, central nervous system effects, intracranial hypertension, autoimmune syndromes, photosensitivity tissue hyperpigmentation) should be considered. Bacterial drug resistance to minocycline foam is possible; therefore, it should only be used as indicated. If superinfection occurs, discontinue use.

Salicylic acid agents are contraindicated in patients with hypersensitivity to salicylates. In concentrations greater than 6%, salicylic products are contraindicated in patients with diabetes mellitus and other

conditions of poor blood circulation such as peripheral vascular disease. Caution should be applied when administering salicylic products in children and adolescents with varicella or influenza due to the potential for Reye's syndrome.

Avoid prolonged usage of salicylic acid over large areas in children and patients with renal impairment or hepatic disease due to the increase the risk of developing salicylism.

Fatalities have rarely occurred due to severe reactions to sulfonamides such as sulfacetamide. Sulfacetamide also contains sodium metabisulfite, which may cause allergic-type reactions in patients.

Tazarotene (Tazorac) can cause local irritation (e.g., blistering, skin desquamation) and hypersensitivity reactions (e.g., urticaria). Tazarotene (Arazlo, Fabior, Tazorac) can cause other local adverse reactions (e.g., application site pain, dryness, erythema, pruritus) and should not be applied to eczematous or sunburned skin. It may also cause photosensitivity.

Tretinoin gel (Atralin) and tretinoin lotion (Altreno) contain soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish.

Concomitant topical acne treatment, as well as cosmetic products with drying effects, should be used with caution, as possible cumulative irritancy may occur.

During the early weeks of therapy, apparent exacerbations of acne may occur. This is caused by the product's action on previously unseen lesions and should not be viewed as a reason to discontinue therapy.

Contact with eyes, eyelids, lips, and mucous membranes should be avoided. Breaks in the skin should also not come into contact with these products.

Avoid fire, flame, and smoking following use of any gel or foam, as they are flammable.

DRUG INTERACTIONS^{194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235}

Concomitant use with cosmetics, medicated or abrasive soaps and cleansers, alcohol, astringents, spices, or lime grind or other agents that have a strong drying effect should be avoided. Benzoyl peroxide potentiates adverse effects seen with tretinoin during concurrent use.

Levels of dapsone and its metabolites, N-acetyl-dapsone (NAD) and dapsone hydroxylamine (DHA), increased when co-administered with trimethoprim-sulfamethoxazole. Temporary local yellow or orange discoloration of the skin and facial hair was seen when topical administration of dapsone was followed by benzoyl peroxide. Concomitant medications such as rifampin, anticonvulsants, and St. John's wort may increase the formation of DHA, which is associated with hemolysis.

Topical erythromycin-containing products and topical clindamycin-containing products should not be administered concomitantly due to the potential antagonism of effect. Other concomitant topical acne therapies should be used with caution in order to prevent cumulative irritancies.

Dapsone can cause elevated methemoglobin levels when used concomitantly with drugs that induce methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, and phenytoin, primaquine.

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, caution should be taken when using clindamycin-containing products with neuromuscular blocking agents.

Minocycline and penicillin coadministration should be avoided. Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. While systemic absorption of topical minocycline foam is minimal, the drug interactions associated with oral minocycline should be considered. Falsely elevated urinary catecholamine levels may be reported on fluorescence testing.

Concomitant use of salicylic acid with other drugs which may contribute to elevated serum salicylate levels (e.g., oral aspirin and other salicylate containing medications, such as sports injury creams) should be avoided.

Sulfonamides (Avar, Avar E, Avar E-LS, Avar LS, BP Cleansing Wash, Klaron, Ovace, Ovace Plus, Ovace Plus Wash, Plexion, SSS 10-5, SulfaCleanse, Sumadan, Sumaxin) are incompatible with preparations containing silver and should not be applied to the same sites as products containing silver salts, including preparations such as silver nitrate, silver sulfadiazine, or mild silver protein.

Tazarotene (Arazlo, Fabior, Tazorac) should be administered with caution if the patient is also taking drugs known to be photosensitizers, such as thiazides, tetracyclines, fluoroquinolones, phenothiazines, or sulfonamides, because of the increased possibility of augmented photosensitivity. Formal drug-drug interaction studies were not conducted with Fabior foam or Arazlo lotion.

ADVERSE EFFECTS^{236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279}

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
adapalene (Differin, Effaclar)	10-60	10-60	10-60	<1-40	10-60	<1
adapalene/ benzoyl peroxide 0.1%/2.5%	1-15	nr	1-13	9-14	nr	nr
adapalene/ benzoyl peroxide 0.3%/2.5% (Epiduo Forte)	1-20	nr	2-15	6-19	nr	nr
azelaic acid (Azelex)	<1	<1	<1	1-5	1-5	nr

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative or all inclusive. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product and are reversible with discontinuation of use. nr = not reported.

Adverse Effects (continued)

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
benzoyl peroxide (Acne Medication) (Acne Spot Treatment) (Advanced Acne Wash) (Benzefoam) (BP) (BP Foam) (BP Foaming Wash) (BPO) (BP Wash) (Cerave Acne Cleanser) (Effaclar Duo) (OC8) (Panoxyl) (Panoxy-4) (Persa-Gel) (Riax)	reported	reported	reported	reported	reported	nr
benzoyl peroxide (BenzePro)	nr	nr	reported	nr	nr	nr
benzoyl peroxide/ clindamycin (Acanya)	2-25	0.1	nr	1-8	1-15	nr
benzoyl peroxide/ clindamycin (BenzaClin)	1	2	12	nr	2	1
benzoyl peroxide/ clindamycin(Neuac)	5-26	2-17	1-15	<1-5	nr	nr
benzoyl peroxide/ clindamycin (Onexton)	<1-28	nr	nr	<1-7	3-15	nr
benzoyl peroxide/ erythromycin (Benzamycin)	reported	reported	3	3	reported	nr
benzoyl peroxide/ hydrocortisone (Vanoxide-HC)	nr	nr	nr	reported	nr	nr

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative or all inclusive. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product and are reversible with discontinuation of use. nr = not reported.

Adverse Effects (continued)

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
clindamycin (Cleocin T)	7-16	7-11	18-23	11	7-11	nr
clindamycin (Clindacin P) (Clindacin PAC) (Clindacin ETZ)	16	11	19	11	7	nr
clindamycin (Clindagel)	nr	0.6	nr	nr	0.6	nr
clindamycin (Evoclin)	nr	nr	1	6	1	nr
clascoterone (Winlevi)	12.2	nr	10.5	4.2	7.7	nr
dapsone (Aczone)	5-9	6-13	3-14	1	1	nr
erythromycin (Erygel) (Ery)	reported	reported	reported	reported	reported	nr
minocycline (Amzeeq)	reported	reported	reported	nr	reported	reported
salicylic acid (Acne Cream) (Acne Pads) (Acne Treatment) (Advanced Acne Spot Treatment) (Clearasil Daily Clear) (Oil-Free Acne Wash) (Rapid Clear)	nr	reported	reported	reported	reported	nr
sodium sulfacetamide (Klaron)	<1	nr	nr	reported	<1	nr
sodium sulfacetamide (Ovace) (Ovace Plus) (Ovace Plus Wash)	nr	nr	nr	reported	nr	nr

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative or all inclusive. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product and are reversible with discontinuation of use. nr = not reported.

Adverse Effects (continued)

Drug	Erythema	Peeling	Dryness	Burning/ Stinging	Itching	Photosensitivity
sodium sulfacetamide/ sulfur (Avar) (Avar E) (Avar E LS) (Avar LS) (BP 10-1) (BP Cleansing Wash) (Plexion) (Rosula) (SSS 10-5) (SulfaCleanse) (Sumadan) (Sumaxin)	reported	reported	reported	reported	reported	reported
tazarotene (Arazlo)	2	2	4	5	1	nr
tazarotene (Fabior)	6	reported	7	reported	1	reported
tazarotene (Tazorac)	10-30	10-30	10-30	10-30	10-30	reported
tretinoin (Altreno)	51	6	29	30/21	35	reported
tretinoin (Atralin)	7	12	16	8	2	1
tretinoin (Avita)	reported	reported	reported	reported	reported	reported
tretinoin (Retin-A)	reported	nr	nr	nr	nr	reported
tretinoin (Retin-A Micro)	reported	reported	reported	reported	reported	reported
tretinoin (Tretin-X)	reported	reported	reported	reported	reported	reported
tretinoin/benzoyl peroxide (Twynéo)	4	4.1	4.9	1.1	1.3	reported
tretinoin/clindamycin (Ziana)	26	17	1	4	4	reported
tretinoin/clindamycin (Veltin)	4	5	6	reported	2	1
trifarotene (Aklief)	reported	reported	reported	reported	reported	reported

Adverse effects data are reported as percentages and obtained from package inserts and are not meant to be comparative or all inclusive. During the first weeks of treatment, cutaneous adverse effects may occur. These effects typically lessen with continued use of the product and are reversible with discontinuation of use. nr = not reported.

SPECIAL POPULATIONS^{280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325}

Pediatrics

The safety and effectiveness of all these products in patients younger than 12 years of age have not been established; the exceptions are benzoyl peroxide, which has been approved for patients as young as 6 years of age, tretinoin (Atralin), which has been studied in children as young as 10 years of age, and adapalene/benzoyl peroxide 0.1%/2.5%, dapsone 7.5% gel (Aczone), minocycline foam (Amzeeq), tazarotene (Arazlo), tretinoin lotion (Altreno), **tretinoin/benzoyl peroxide (Twynéo)**, trifarotene (Aklief) in children as young as 9 years of age. Safety of dapsone 5% gel has not been studied in patients younger than 12 years.

Pregnancy

Previously, tazarotene (Fabior, Tazorac) was classified as Pregnancy Category X; however, its labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). There are no data on the use of tazarotene (Arazlo) in pregnant women, but its use is contraindicated in this population. Tazarotene, as a retinoid, is a teratogenic substance; it is not known what level of exposure causes teratogenicity in humans. Other retinoids may cause fetal harm in pregnant women.

Tretinoin (Atralin, Avita, Retin-A, Retin-A Micro, Tretin-X), adapalene (Differin, Effaclar), and tretinoin/clindamycin (Veltin, Ziana) are Pregnancy Category C. The labeling for minocycline foam (Amzeeq), tretinoin lotion (Altreno), and **tretinoin/benzoyl peroxide (Twynéo)** comply with the PLLR and state drug-associated risk of adverse maternal or fetal outcomes have not been established based on available data. Labeling for trifarotene (Aklief) states that available data have not identified a drug-related risk of major maternal or fetal outcomes.

Previously Pregnancy Category C, labeling for dapsone (Aczone) and benzoyl peroxide/clindamycin (Acanya, Onexton) have been updated to comply with PLLR and advises that there are no available data to inform of drug-related risks to the fetus if used during pregnancy.

Previously Pregnancy Category B, labeling for clindamycin (Cleocin T) has been updated to comply with the PLLR and informs that systemic administration of clindamycin during the second and third trimesters has not been associated with an increased likelihood of congenital abnormalities; however, there are not sufficient studies regarding its use during the first trimester of pregnancy, and it should only be used at this time if clearly needed.

The safety and effectiveness of salicylic acid in pregnancy women is not well studied. Salicylic acid should only be used during pregnancy if the potential benefits to the mother outweigh the potential risk to the fetus.

There are no human data available regarding the potential for fetal harm with the use of clascoterone (Winlevi) during pregnancy or with breast feeding. Therefore, the risks and benefits of treatment with clascoterone should be considered in women that are pregnant or nursing.

All other reviewed agents are Pregnancy Category C, with the exception of single component clindamycin and erythromycin products, which are Pregnancy Category B.

Antibiotics, like clindamycin, can cause adverse effects on a breastfed infant’s gastrointestinal flora; an alternative may be preferred in breastfeeding women.

Patients with deficiency of glucose-6-phosphate dehydrogenase (G6PD)

A double-blind, randomized, vehicle-controlled, crossover study with patients aged 12 years and older with G6PD deficiency and acne vulgaris reported a decrease in hemoglobin concentration by 0.32 g/dL from baseline to 2 weeks during treatment with dapsone 5% gel treatment.³²⁶ No other changes in other laboratory parameters were reported up to 12 weeks with continued treatment. No clinical signs or symptoms of hemolytic anemia were noted.

DOSAGES^{327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379}

Drug	Instructions	Availability
adapalene (Differin, Effaclar)	apply thin film to affected area(s) once daily at after washing as directed	0.1% cream, lotion (Rx-only) 0.1 % gel (tube) (Differin, Effaclar) (OTC only) 0.1% topical solution (Rx-only) 0.3% gel pump (Rx-only)
adapalene/benzoyl peroxide (Epiduo Forte)	apply thin film to affected areas once daily after washing	0.1/2.5% gel pump (generic only) 0.3/2.5% gel pump (Epiduo Forte)
azelaic acid (Azelex)	apply to affected areas	20% cream
benzoyl peroxide	apply once or twice daily as directed	10% cream 2.5%, 5%, 10% gel* 3%, 4%, 5%, 6%, 7% (Rx-only), 9%, 10 % cleanser* 5.3%, 9.8% emollient foam 10% lotion*
benzoyl peroxide (Acne Medication)	apply 1 to 3 times daily as directed	5%, 10% gel* 5%, 10% lotion*
benzoyl peroxide (Acne Spot Treatment)	apply 1 to 3 times daily as directed	2.5% cream*
benzoyl peroxide (Acne Treatment)	apply 1 to 3 times daily as directed	10% cream, cleanser, gel
benzoyl peroxide (Advanced Acne Wash)	apply once or twice daily as directed	4.4% cleanser ER*
benzoyl peroxide (Benzefoam)	apply 1 to 3 times daily as directed	5.3% foam*
benzoyl peroxide (BenzePro)	apply once to 3 times daily as directed	7% cleanser 5.2%, 5.3%, 9.8% foam 6% towelette
benzoyl peroxide (BP)	apply 1 to 3 times as directed	5%, 10% gel*

* Products available without prescription (over-the-counter). Other products are available by prescription only.

Dosages (continued)

Drug	Instructions	Availability
benzoyl peroxide (BP Foam)	apply 1 to 3 times as directed	5.3%, 9.8% foam*
benzoyl peroxide (BP Foaming Wash)	apply 1 to 3 times as directed	10% cleanser*
benzoyl peroxide (BP Wash)	apply 1 to 3 times as directed	2.5%*, 5%, 7%*, 10% cleanser
benzoyl peroxide (BPO)	apply once to twice daily as directed	4%, 8% gel 6%, towelette
benzoyl peroxide (Clearasil Daily Clear) (Clearasil Ultra)	apply once to twice daily as directed	10% cream*
benzoyl peroxide (Cerave Acne Cleanser)	apply once to twice daily as directed	4% cleanser*
benzoyl peroxide (Daylogic Acne Treatment)	apply 1 to 3 times per day as directed	10% gel
benzoyl peroxide (Effaclar Duo)	apply as directed	5.5% solution*
benzoyl peroxide (Enzoclear)	apply 1 to 3 times per day or as directed	9.8% foam
benzoyl peroxide (OC8)	apply once or twice daily as directed	7% gel*
benzoyl peroxide (Panoxyl)	apply once or twice daily as directed	3% cream* 4% cleanser* 10% bar, cleanser*
benzoyl peroxide (Persa-Gel)	apply once or twice daily as directed	10% gel*
benzoyl peroxide (Riax)	apply 1 to 3 times as directed	5.5%, 9.5% foam* 9.5% towelette*
benzoyl peroxide/clindamycin (Acanya)	apply a pea size amount once daily to the face	2.5/1.2% gel pump
benzoyl peroxide/clindamycin (BenzaClin)	apply twice daily or as directed	5/1% gel, gel pump
benzoyl peroxide/clindamycin (Neuac)	apply once daily, in the evening, after washing as directed	5/1.2% gel
benzoyl peroxide/clindamycin (Onexton)	apply pea sized amount to the face once daily	1.2/3.75% gel, gel pump
benzoyl peroxide/ erythromycin (Benzamycin)	apply twice daily as directed	5/3% gel
benzoyl peroxide/ hydrocortisone (Vanoxide-HC)	apply as directed	5/0.5% suspension benzoyl peroxide bulk powder and hydrocortisone

* Products available without prescription (over-the-counter). Other products are available by prescription only.

Dosages (continued)

Drug	Instructions	Availability
clindamycin	apply twice daily to affected areas	1% foam, gel, lotion, solution, med swab
clindamycin (Cleocin T)	apply twice daily to affected areas	1% gel (generic only), solution (generic only) 1% lotion
Clindamycin (Clindacin ETZ, Clindacin P)	apply twice daily to affected areas	1% med swab (pledget)
clascoterone (Winlevi)	apply twice daily as directed	1% cream
clindamycin (Clindagel)	apply once daily to affected areas	1% gel
clindamycin (Evoclin)	apply once daily to affected areas	1% foam
dapsone (Aczone)	5%- apply pea-sized amount twice a day to affected areas 7.5%- apply pea-sized amount to face once daily; can also apply thin layer to other affected areas once daily	5% gel (tube) 7.5% gel (pump)
erythromycin	apply twice daily to affected areas	2% gel, med pad, solution
erythromycin (Ery)	apply to affected area twice daily (morning and evening as directed)	2% med pad
erythromycin (Erygel)	apply once or twice daily to affected area(s) as directed	2% gel
minocycline (Amzeeq)	apply to affected area(s) once daily	4% topical foam
salicylic acid (Clearasil Daily Clear)	apply as directed to affected areas	1%, 2% med pad* 2% cleanser*
salicylic acid (Oil-Free Acne Wash, Effaclar Medicated Gel Cleanser)	apply as directed to affected areas twice daily; rinse	2% cleanser*
salicylic acid (Advanced Acne Spot Treatment)	apply to entire affected area with a thin layer 1 to 3 times a day.	2% ointment*
salicylic acid (Acne Pads) (Medicated Cleansing) (Rapid Clear)	apply as directed to affected areas	2% med pad*
salicylic acid (Acne Cream)	apply as directed to affected areas	10% cream*
salicylic acid/benzoyl peroxide (Effaclar Acne System)	apply as directed to affected areas	2% salicylic acid cleanser + 0.5% salicylic acid solution + 5.5% benzoyl peroxide*

* Products available without prescription (over-the-counter). Other products are available by prescription only.

Dosages (continued)

Drug	Instructions	Availability
sodium sulfacetamide	apply as directed to affected areas	10% cleanser, cleanser gel, lotion, shampoo
sodium sulfacetamide (Klaron)	apply twice daily to affected areas	10% lotion
sodium sulfacetamide (Ovace)	apply once or twice daily as directed	10% cleanser
sodium sulfacetamide (Ovace Plus)	foam: apply 1 to 3 times daily to affected areas as directed cleanser ER, cream, lotion, shampoo: apply twice daily (morning and evening) to affected area as directed	9.8% foam, lotion, shampoo 10% cream 10% shampoo 10% cleanser ER
sodium sulfacetamide (Ovace Plus Wash)	apply once or twice daily as directed	10% cleanser gel ER
sodium sulfacetamide/sulfur	apply 1 to 3 times daily to affected areas as directed	8/4% suspension 9/4% cleanser 9.8/4.8% cleanser, cream, lotion 10% lotion 10/2% cream, cleanser 10/4% med pads 10/5% lotion, cleanser, cream, foam, gel, suspension
sodium sulfacetamide/sulfur (Avar)	apply 1 to 3 times daily to affected areas as directed	9.5/5% med pad 10/5% cleanser
sodium sulfacetamide/sulfur (Avar E) (Avar E-Green)	apply 1 to 3 times daily to affected areas as directed	10/5% cream
sodium sulfacetamide/sulfur (Avar E-LS)	apply 1 to 3 times daily to affected areas as directed	10/2% cream
sodium sulfacetamide/sulfur (Avar LS)	apply 1 to 3 times daily to affected areas as directed	10/2% cleanser, foam, med pad
sodium sulfacetamide/sulfur (BP 10-1)	apply 1 to 3 times daily to affected areas as directed	10/1% cleanser
sodium sulfacetamide/sulfur (Plexion)	apply to affected area as directed	9.8/4.8% cream, cleanser, med pad, lotion, cleansing cloth
sodium sulfacetamide/sulfur (Rosula)	apply once or twice daily as directed	10/4.5% cleanser 10/5% towelette
sodium sulfacetamide/sulfur (SSS 10-5)	apply 1 to 3 times daily to affected areas as directed	10/5% cream, foam

* Products available without prescription (over-the-counter). Other products are available by prescription only.

Dosages (continued)

Drug	Instructions	Availability
sodium sulfacetamide/sulfur (SulfaCleanse) (Sumaxin TS)	apply once or twice daily as directed	8/4% suspension In a vehicle containing green tea & aloe
sodium sulfacetamide/sulfur (Sumadan)	apply once or twice daily as directed	9/4.5% cleanser
sodium sulfacetamide/sulfur (Sumaxin)	apply once or twice daily as directed	10/4% med pads 9/4% cleanser
sodium sulfacetamide/ sulfur/urea vehicle (BP 10-1 Cleansing Wash)	apply once or twice daily as directed	10/4/10%, 10/5/10% cleanser
sulfur (Palmers Skin Success, Sulfo-Lo)	use daily to cleanse affected skin or as directed by a physician	3% cleansing bar (OTC)
tazarotene	apply a thin film once daily in the evening to affected areas after washing	0.1% cream
tazarotene (Arazlo)	apply a thin layer once daily	0.045% lotion
tazarotene (Fabior)	apply a thin layer once daily in the evening	0.1% foam
tazarotene (Tazorac)	apply a thin film once daily in the evening to affected areas	0.05%, 0.1% cream, gel
tretinoin	apply once daily in the evening to affected area	0.025%, 0.05%, 0.1% cream 0.01%, 0.025%, 0.05% gel
tretinoin (Altreno)	apply a thin layer once daily	0.05% lotion
tretinoin (Atralin)	apply once daily at bedtime to affected areas	0.05% gel
tretinoin (Avita)	apply once daily in the evening to affected area	0.025% cream, gel
tretinoin (Refissa)	apply once daily in the evening to affected area	0.05% cream
tretinoin (Retin-A)	apply once daily in the evening to affected area	0.025%, 0.05%, 0.1% cream 0.01%, 0.025% gel
tretinoin (Tretin-X)	apply a thin layer once daily, before bedtime, to affected areas	0.025%, 0.05%, 0.1%, combo package 0.075% cream
tretinoin microspheres	apply a thin layer once daily, before bedtime, to affected areas	0.04%, 0.1% gel, gel pump
tretinoin microspheres (Retin-A Micro)	apply a thin layer once daily, before bedtime, to affected areas	0.04%, 0.1% gel 0.04%, 0.06%, 0.08%, 0.1% gel pump

* Products available without prescription (over-the-counter). Other products are available by prescription only.

Dosages (continued)

Drug	Instructions	Availability
tretinoin/benzoyl peroxide (Twynéo)	apply once daily	0.1%/3% cream
tretinoin/clindamycin	apply once daily at bedtime to face	1.2/0.025% gel
tretinoin/clindamycin (Ziana)	apply once daily at bedtime to face g	1.2/0.025% gel
tretinoin/clindamycin (Veltin) [†]	apply once daily in the evening to	1.2/0.025% gel
trifarotene (Aklief)	apply a thin layer to the affected area(s) once daily, in the evening	0.005% cream

* Products available without prescription (over-the-counter). Other products are available by prescription only.

Clindacin ETZ, Clindacin P, Clindacin PAC, Ery, Neuac, Refissa, Tretin-X were FDA approved under ANDAs (generics).

Before application of these products, the affected skin should be thoroughly washed, rinsed with warm water, and patted dry.

Benzamycin requires the addition of ethyl alcohol and must be refrigerated following reconstitution.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and acne vulgaris. Randomized controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There were many studies found using these criteria. Only comparative studies were included, and studies of the active drug compared to placebo or vehicle were not included. Unacceptable data were determined to be those studies with any of the following characteristics: low number of patients enrolled, comparator drug not available in the US, manufacturer-sponsored, open-label, pooled data, unavailable strengths in US, use of different formulations of the same active ingredient, inadequate treatment duration, or split-face treatment. Many studies use the investigator-blinded design rather than using the double-blinded method.

adapalene (Differin) versus benzoyl peroxide/clindamycin versus benzoyl peroxide/clindamycin plus adapalene

A multicenter, parallel-group, single-blind study of 109 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel, adapalene 0.1% gel, and the combination.³⁸⁰ Primary endpoints were inflammatory, noninflammatory, and total lesion counts at weeks 2, 4, 8, and 12. Lesion count reduction and percentage change at week 12 were highest in the combination therapy group (p=NS) and lowest in the adapalene group (p=NS). Taken individually, the combination group had higher reductions in noninflammatory lesions and total lesions compared to the adapalene group (both p<0.05). At week 12, there were no significant differences among groups with regard to erythema, dryness, or peeling. A separate analysis of the adverse events showed that the patients in the combination therapy group had less erythema than patients in the adapalene group (p<0.05).

adapalene (Differin) versus tazarotene (Tazorac)

A multicenter, double-blind, randomized, parallel-group study enrolled 164 patients with mild to moderate facial acne vulgaris to receive 15 weeks of treatment with alternate-day tazarotene 0.1% gel and vehicle gel on the intervening evenings or once daily adapalene 0.1% gel.³⁸¹ Both regimens were comparably effective with no significant between-group differences in efficacy measures. A total of 74% of tazarotene-treated subjects and 73% of adapalene-treated subjects achieved at least a 50% improvement in their acne. In addition, there were no clinically significant differences in tolerability. It appears that tazarotene treatment can be useful even in patients whose compliance may be suboptimal.

The efficacy and tolerability of tazarotene 0.1% gel and adapalene 0.1% gel were compared in a multicenter, double-blind, randomized, parallel-group study in 145 patients with mild to moderate facial acne vulgaris.³⁸² Both treatments were applied once daily in the evenings for up to 12 weeks. Treatment with tazarotene was associated with a significantly greater incidence of treatment success (≥50% global improvement with 78% versus 52%; p=0.002), significantly greater reductions in overall disease severity (p<0.0001), non-inflammatory lesion count (p<0.0001), and inflammatory lesion count (p=0.0002) compared with adapalene. In the early weeks of treatment, tazarotene was associated with greater levels of burning, pruritus, erythema, and peeling compared with adapalene (p<0.01); however, at the end of treatment, patients considered both treatments to be comparably well tolerated.

adapalene (Differin) versus tretinoin

A dose range effect of 2 concentrations of adapalene gel as acne treatment was evaluated, as well as a comparison of adapalene 0.1% gel with tretinoin 0.025% gel in the treatment of acne patients using two multicenter, investigator-masked, parallel group studies.³⁸³ In the dose range study, 89 patients were enrolled, and 591 patients were in the concurrent controlled studies. Adapalene 0.1% gel was significantly more effective in treating acne lesions than adapalene gel 0.03%. Adapalene gel 0.1% was significantly more effective than tretinoin 0.025% gel in 1 study and of the same effectiveness in the other study. Adapalene gel was better tolerated than tretinoin gel.

The 10-week, multicenter, randomized, investigator-masked, active-controlled, parallel-group study compared adapalene 0.1% gel with tretinoin 0.05% cream in 409 patients with mild to moderate acne vulgaris.³⁸⁴ Adapalene 0.1% gel demonstrated equivalent efficacy in reduction of acne lesion counts and global improvement of acne severity over 10 weeks. Adapalene 0.1% gel was significantly better tolerated than tretinoin cream 0.05% in terms of erythema, dryness, desquamation, and stinging/burning.

To determine the tolerability and efficacy of adapalene 0.1% gel versus tretinoin 0.1% microsphere gel in 168 patients with acne vulgaris, a 12-week, multicenter, randomized, controlled, investigator-masked, parallel-group study was conducted.³⁸⁵ The efficacy of adapalene 0.1% gel was comparable to that of tretinoin 0.1% microsphere gel, and both treatments had similar onset of action. Cutaneous tolerability was noted in both groups, with scores significantly better with adapalene 0.1% gel than with tretinoin 0.1% microsphere gel. There were significantly fewer treatment-related adverse events reported with adapalene 0.1% gel.

A randomized, multicenter, investigator-masked study was conducted in 105 patients with mild to moderate acne vulgaris to compare the efficacy and safety of adapalene 0.1% gel with tretinoin 0.025% gel after 3 months of treatment.³⁸⁶ In terms of efficacy, adapalene gel was found to be superior to tretinoin gel after 1 week of treatment, with respect to reduction in inflammatory lesion counts (32% versus 17%, respectively; $p=0.001$), total lesion counts (28% versus 22%; $p=0.042$), and global severity grade (28% versus 16%; $p=0.001$). No significant differences between the 2 treatments were found after 12 weeks of treatment for any of these variables. Evaluation of facial skin tolerance parameters showed significant differences between the 2 treatments in favor of adapalene for dryness, erythema, immediate and persistent burning, and pruritus for at least 1 time point. Quality of life scores improved more rapidly in the adapalene group than in the tretinoin group.

A study was designed to compare the efficacy and safety of adapalene 0.1% gel once daily and tretinoin 0.025% gel once daily in the treatment of facial acne vulgaris.³⁸⁷ A total of 323 patients were enrolled for 12 weeks in an investigator-masked, randomized, parallel-group, multicenter trial. Starting at weeks 2 and 4, adapalene produced greater lesion reductions than did tretinoin for all lesion types. By week 12, the mean percent reduction in the different lesion counts was 49% versus 37% for total lesions ($p<0.01$); 46% versus 33% for non-inflammatory lesions ($p=0.02$); and 48% versus 38% for inflammatory lesions ($p=0.06$) in adapalene (Differin) and tretinoin treatment groups, respectively. Adverse effects were limited to a mild dermatitis occurring in both treatment groups.

adapalene 1%/benzoyl peroxide 2.5% versus adapalene (Differin) versus benzoyl peroxide

A multicenter, double-blind, randomized study involving randomized 517 subjects to adapalene 1%/benzoyl peroxide 2.5% (BPO) gel, adapalene 0.1% in vehicle gel, BPO 2.5% in vehicle gel, or vehicle gel alone. The median age of these subjects was 15 years and 60% were males.³⁸⁸ At baseline, subjects had between 20 to 50 inflammatory lesions and 30 to 100 non-inflammatory lesions. The majority of subjects had a baseline Investigator's Global Assessment (IGA) of 'moderate', which corresponded to more than half of the face being involved and including many comedones, papules, and pustules. The efficacy results at week 12 showed a two-grade IGA improvement and 'clear' or 'almost clear' rating for 21.5% of the adapalene/BPO group, 12.2% of the adapalene group, 12.1% of the BPO group, and 5.6% of the vehicle group.

A 12-week, randomized, double-blind, parallel-group, active- and vehicle-controlled, multicenter trial compared adapalene 0.1%/benzoyl peroxide 2.5% (BPO) gel, adapalene 0.1% in vehicle gel, BPO 2.5% in vehicle gel, or vehicle gel alone in 1,668 patients with moderate facial acne.³⁸⁹ At 12 weeks, the combination adapalene-BPO gel showed a significantly higher success rate (the percentage of participants with IGA of acne severity rated clear or almost clear; $p\leq 0.006$) and a greater percentage reduction in all acne lesion counts ($p\leq 0.017$) compared with the other treatment groups. A significant early treatment effect of adapalene-BPO combination gel at week 1 compared with adapalene

monotherapy and vehicle also was observed for all lesion count reductions ($p < 0.001$). Adverse events were similar in all groups.

adapalene 3%/benzoyl peroxide 2.5% (Epiduo Forte) and adapalene 1%/benzoyl peroxide 2.5%

A double-blind study compared adapalene 3%/benzoyl peroxide 2.5% gel ($n=217$) to vehicle gel ($n=69$) in patients with acne vulgaris.³⁹⁰ The study also randomized patients to adapalene 1%/benzoyl peroxide 2.5% gel ($n=217$). At baseline, 50% of subjects were graded as “moderate” (Grade 3) and 50% were graded as “severe” (Grade 4) on the Investigator’s Global Assessment (IGA) scale. At Week-12, 33.7%, 27.3%, and 11% of patients on 3%/2.5% gel, 1%/2.5% gel, and vehicle gel, respectively experienced at least a 2-grade improvement based on the IGA. There was also a significant improvement in reduction of both inflammatory and non-inflammatory lesion counts with both adapalene/benzoyl peroxide formulations as compared to vehicle. This study was not designed or powered to compare the efficacy of adapalene benzoyl peroxide gel 3%/2.5% gel to the 1%/2.5% gel.

benzoyl peroxide/clindamycin (Neuac) versus benzoyl peroxide versus clindamycin

Five randomized, double-blind clinical studies evaluated the efficacy of benzoyl peroxide 5%/clindamycin 1.2% combination as compared to benzoyl peroxide, clindamycin, and vehicle.³⁹¹ There were a total of 1,319 patients within the 5 studies. 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 going to bed. Patients were evaluated and their acne lesions were counted at each clinical visit: weeks 2, 5, 8, and 11. The primary efficacy measures were the lesion counts and the investigator’s global assessment evaluated at week 11. Benzoyl peroxide and clindamycin 5%/1.2% gel applied once daily for 11 weeks, was significantly more effective than vehicle, benzoyl peroxide, and clindamycin in the treatment of inflammatory lesions of moderate to moderately severe facial acne vulgaris in 3 of the 5 studies (Studies 1, 2, and 5).

benzoyl peroxide/clindamycin (Acanya) versus benzoyl peroxide versus clindamycin

The clinical safety and efficacy of benzoyl peroxide (BPO)/clindamycin gel were established in 2 identical, double-blind, randomized, controlled, 12-week, 4-arm studies in which vehicle gels were used as the comparators.^{392,393} A total of 2,813 patients with moderate to severe acne vulgaris aged 12 years or older were randomized to receive BPO/clindamycin, BPO, clindamycin, or vehicle. Safety and efficacy (inflammatory and noninflammatory lesion counts) were evaluated using Evaluator Global Severity Score and subject self-assessment. BPO/clindamycin demonstrated superiority to each individual ingredient and vehicle in reducing both inflammatory and non-inflammatory lesions and acne severity. Visibly greater improvement was observed by patients with BPO/clindamycin as early as week 2. No substantive differences were seen in tolerability among treatment groups; less than 1% of patients discontinued treatment because of adverse events.

benzoyl peroxide/clindamycin (BenzaClin) versus benzoyl peroxide versus benzoyl peroxide/erythromycin (Benzamycin)

In the randomized, 10-week, multicenter, single-blind trial, 492 patients with moderate to moderately severe acne were treated twice daily with benzoyl peroxide 5%/clindamycin 1%, benzoyl peroxide 5%, or benzoyl peroxide 5%/erythromycin 3% and assessed every 2 weeks.³⁹⁴ Compared with benzoyl peroxide, benzoyl peroxide/clindamycin demonstrated significantly greater reductions in inflammatory lesions ($p=0.04$) and significantly greater overall improvement as assessed by physicians ($p \leq 0.04$) and

patients ($p < 0.001$). Benzoyl peroxide/clindamycin was not significantly more efficacious than benzoyl peroxide/erythromycin. Dry skin was the most frequent adverse event with all 3 therapies.

benzoyl peroxide/clindamycin (BenzaClin) versus benzoyl peroxide versus clindamycin

In a 10-week, multicenter, double-blind trial, 480 patients with moderate to moderately severe acne were randomized to receive twice daily treatment with benzoyl peroxide 5% plus clindamycin 1%, benzoyl peroxide 5%, clindamycin 1%, or vehicle.³⁹⁵ Significantly greater reductions in the number of inflammatory and total lesions were demonstrated in patients using combination therapy compared with those using any of the individual components. Both physicians' and patients' global evaluations showed significantly greater improvements with the combination therapy than with individual components. Dry skin was the most frequent adverse event, occurring to a similar extent in the combination and benzoyl peroxide treatment groups.

A topical gel combining benzoyl peroxide 5% and clindamycin 1% was evaluated in a 10-week, randomized, double-blind trial involving 287 patients with moderate to moderately severe acne.³⁹⁶ The combination demonstrated significantly greater reductions in inflammatory lesions than either of its components alone or vehicle. Significantly greater reductions in comedones and improvements in both physicians' and patients' global evaluations were obtained with the combination compared to clindamycin or vehicle. The reduction in comedones and the global improvements were similar between the combination and benzoyl peroxide. The incidence of dry skin in the combination group was similar to that found with benzoyl peroxide.

clindamycin versus adapalene (Differin)/clindamycin

A total of 300 patients with acne entered a multicenter, randomized, investigator-blinded study comparing the efficacy and safety of adapalene 0.1% gel combined with clindamycin topical solution 1% versus clindamycin topical solution 1% alone.³⁹⁷ A statistically significant greater reduction was observed from week 4 until week 12 in total lesion counts and from week 8 on for inflammatory and non-inflammatory lesion counts during the initial treatment for combination therapy compared with monotherapy. In the second part of the study (weeks 12 to 24) which was completed by 241 subjects, the efficacy and safety of adapalene alone as maintenance therapy were investigated. Results at week 24 for the reduction in lesion counts during the maintenance phase were statistically significant in favor of adapalene (41.6%) compared with an increase for all lesion counts in the control group (92.1%). Adapalene alone or in combination with clindamycin topical solution was well tolerated.

A multicenter, randomized, investigator-blinded study evaluated the efficacy and tolerability of adapalene 0.1% gel plus clindamycin 1% lotion compared with clindamycin 1% lotion plus vehicle for the treatment of mild to moderate acne vulgaris in 249 patients.³⁹⁸ Clindamycin was applied twice daily and adapalene or vehicle gel once daily for 12 weeks. Significantly greater reductions of total ($p < 0.001$), inflammatory ($p = 0.004$), and noninflammatory lesions ($p < 0.001$), were seen in the clindamycin/adapalene group than in the clindamycin/vehicle group. These significant treatment effects were observed as early as week 4 for both non-inflammatory and total lesion counts. The worst scores for scaling ($p < 0.05$), dryness ($p < 0.01$), and stinging/burning ($p < 0.05$) were higher in the clindamycin/adapalene group than in the clindamycin/vehicle group.

clindamycin/tretinoin (Veltin) versus clindamycin versus tretinoin

The efficacy and safety of clindamycin 1.2% gel and tretinoin 0.025% solubilized in an aqueous-based gel were evaluated in a randomized, double-blind, vehicle-controlled study in 1,649 patients with facial acne vulgaris for 12 weeks.³⁹⁹ The reduction in absolute number of total lesions was greater for clindamycin/tretinoin gel versus clindamycin 1.2% gel and tretinoin 0.025% gel. The reduction in total lesions (55% versus 49%, $p \leq 0.004$) and non-inflammatory lesions (51% versus 43%, $p \leq 0.001$) was greater for clindamycin/tretinoin versus clindamycin, as well as the reduction in total lesions (55% versus 51%, $p < 0.05$) and inflammatory lesions (61% versus 55%, $p \leq 0.004$) versus tretinoin. At 12 weeks, more patients achieved $\geq 40\%$ global improvement with clindamycin/tretinoin than with clindamycin or tretinoin (36% versus 27% and 26%, $p \leq 0.001$ respectively). All 3 regimens were generally well tolerated, although treatment-related application site reactions occurred more frequently with tretinoin and clindamycin/tretinoin (7% and 5%, respectively). This study was supported through a grant from Stiefel.

dapsone (Aczone) plus adapalene gel (Differin) versus dapsone plus benzoyl peroxide versus dapsone plus moisturizer

A 12-week, randomized, double-blind study of 301 patients with acne evaluated the safety and efficacy of dapsone 5% gel when used in combination with adapalene gel 0.1%, benzoyl peroxide gel 4%, or moisturizer.⁴⁰⁰ Dapsone gel combined with any of the 3 additional treatments reduced the mean number of inflammatory lesions. However, the reduction of inflammatory lesions was not significant when dapsone was used in combination with adapalene gel or with benzoyl peroxide gel compared to the dapsone plus moisturizer combination group ($p = 0.052$ for both versus moisturizer combination). Patients treated with dapsone gel combined with adapalene gel had a significantly better response in reduction in non-inflammatory and total acne lesion count compared to patients who received the moisturizer combination. All treatments were well tolerated.

benzoyl peroxide/clindamycin plus adapalene (Differin) versus benzoyl peroxide plus tretinoin microsphere (Retin-A Micro)

A multicenter, randomized, single-blind study of 353 patients measured the efficacy and safety of benzoyl peroxide 5%/clindamycin 1% gel in combination with either adapalene 0.1% gel or tretinoin microsphere 0.04% or 0.1% gel.⁴⁰¹ The primary endpoint was investigator global assessment, including variables of lesions counts, global disease severity, and disease signs and symptoms. A trend toward greater reduction in lesions at all time points was seen in the tretinoin 0.04% combination patients, but the difference did not reach statistical significance. The same trend was seen in global disease severity and disease signs and symptoms; none of the differences were statistically significant. Adverse events were minimal and mild in each group.

erythromycin versus clindamycin

A 12-week, investigator-masked, randomized, parallel-group comparison of a gel formulation of erythromycin 2% with clindamycin 1% solution was performed in 102 patients with mild to moderate facial acne vulgaris.⁴⁰² Both agents were administered twice daily. Both medications significantly reduced the numbers of papules and open and closed comedones. No significant differences in lesion count reductions were detected between the treatment groups after 8 and 12 weeks of treatment.

tazarotene (Tazorac) plus benzoyl peroxide versus tazarotene plus erythromycin/benzoyl peroxide (Benzamycin Pak) versus tazarotene plus clindamycin

A multicenter, investigator-masked, randomized, parallel-group study was performed in 440 patients with mild to moderate facial acne vulgaris to compare the efficacy and tolerability of tazarotene monotherapy with 3 combination regimens.⁴⁰³ Patients received tazarotene plus benzoyl peroxide gel, tazarotene plus erythromycin/benzoyl peroxide gel, or tazarotene plus clindamycin phosphate lotion. The only combination therapy to achieve a significantly greater global improvement than tazarotene monotherapy was tazarotene plus clindamycin. For reducing noninflammatory lesions specifically, none of the combination regimens offered significant benefit over tazarotene monotherapy. For reducing inflammatory lesions, tazarotene plus erythromycin/benzoyl peroxide was significantly more efficacious than all the other regimens. Tazarotene plus clindamycin and tazarotene plus benzoyl peroxide reduced the incidence of adverse effects compared with tazarotene monotherapy; however, the difference was not statistically significant.

tazarotene (Tazorac) plus clindamycin versus tretinoin plus clindamycin

A randomized, investigator-blinded, parallel group, multicenter study compared tazarotene 0.1% cream plus clindamycin 1% gel to tretinoin 0.025% gel plus clindamycin 1% gel in 150 patients with facial acne vulgaris.⁴⁰⁴ At 12 weeks, the reduction in lesion counts was greater for tazarotene/clindamycin versus tretinoin/clindamycin for both the non-inflammatory lesion count (71% versus 52%, $p \leq 0.01$) and the inflammatory lesion count (77% versus 67%, $p = 0.053$). More patients achieved $\geq 50\%$ global improvement and $\geq 75\%$ global improvement with tazarotene/clindamycin than with tretinoin/clindamycin (88% versus 75%, $p \leq 0.05$ and 66% versus 52% $p = 0.10$, respectively) at week 12. Both regimens were generally well tolerated. This study was supported through a grant from Allergan.

tazarotene (Tazorac) versus tretinoin

The efficacy and tolerability of tazarotene 0.1% gel and tretinoin 0.1% microsphere gel were evaluated in a multicenter, double-blind, randomized, parallel-group study in 169 patients with mild to moderate inflammatory facial acne vulgaris for 12 weeks.⁴⁰⁵ Both agents were associated with significant reductions from baseline in the non-inflammatory and inflammatory lesion counts. Tazarotene treatment was associated with a significantly greater incidence of treatment success (defined as $\geq 50\%$ global improvement [67% versus 49%; $p = 0.03$]) and significantly greater reductions in overall disease severity (36% versus 26%; $p = 0.02$) and non-inflammatory lesion count (60% versus 38% at week 12; $p = 0.02$) than tretinoin microsphere treatment. Both drugs were well tolerated.

A multicenter, double-blind, randomized, parallel-group study that compared the efficacy and tolerability of tazarotene and tretinoin was performed in 143 patients with mild to moderate facial acne vulgaris.⁴⁰⁶ Patients were randomized to receive tazarotene 0.1% gel or tretinoin 0.025% gel once daily for 12 weeks. Tazarotene 0.1% gel was more effective than tretinoin 0.025% gel in reducing the open comedone count ($p \leq 0.05$) and the total non-inflammatory lesion count ($p \leq 0.05$). The total inflammatory lesion count was similar ($p = \text{NS}$). At some timepoints, tazarotene was associated with increased irritation, but peeling, erythema, dryness, burning, and itching never exceeded trace levels.

A 12-week, investigator-blinded, randomized, parallel-design trial compared the safety and efficacy of tretinoin microsphere gel 0.04% to tazarotene cream 0.05% in mild to moderate facial acne vulgaris.⁴⁰⁷ Efficacy measurements included IGA, lesion counts, and subject self-assessment of acne signs and symptoms. Efficacy was generally comparable between treatment groups, although tretinoin provided

more rapid results in several parameters. IGA showed a more rapid mean change from baseline at week 4 in the tretinoin group (-0.18 versus -0.05 in the tazarotene group). Tretinoin improved papules more rapidly. At week 4, the mean percentage change from baseline in open comedones was statistically significant at -64% in the tretinoin group ($p=0.0039$, within group) versus -19% in the tazarotene group (not statistically significant within the group; $p=0.1875$). Beginning with week 4, skin dryness, peeling, and pruritus were significantly lower in the tretinoin group. Both groups had a low incidence of adverse events.

META-ANALYSES

A meta-analysis evaluating efficacy of benzoyl peroxide (BPO), clindamycin, BPO/salicylic acid, and combination of BPO/clindamycin using the Cochrane collaboration guidelines included a total of 23 studies including 7,309 patients with acne.⁴⁰⁸ At 2 to 4 weeks, BPO/salicylic acid had a statistically greater percentage of lesion reductions over other groups (weighted mean inflammatory lesion reduction: BPO 33.4%, clindamycin 21.5%, BPO/salicylic acid 55.2%, BPO/clindamycin 40.7%, placebo 7.3%; weighted mean non-inflammatory lesion reduction: BPO 19.1%, clindamycin 10%, BPO/salicylic acid 42.7%, BPO/clindamycin 26.2%, placebo 6.7%). At 10- to 12-week endpoints, BPO/salicylic acid and BPO/clindamycin were similar (weighted mean inflammatory lesion reduction: BPO 43.7%, clindamycin 45.9%, BPO/salicylic acid 51.8%, BPO/clindamycin 55.6%, placebo 26.8%; weighted mean non-inflammatory lesion reduction: BPO 30.9%, clindamycin 32.6%, BPO/salicylic acid 47.8%, BPO/clindamycin 40.3%, placebo 17%).

A systematic review of topical retinoids used to treat acne vulgaris in patients at least 12 years of age was conducted based on a PubMed and Embase search of studies published between January 1, 2008 and September 1, 2018.⁴⁰⁹ A total of 54 studies met the inclusion criteria. The analysis found no significant difference in efficacy between tretinoin and tazarotene. Adverse effects were reported in 62% of patients treated with tretinoin 0.05% compared with 19% of those treated with adapalene 0.1% and 40% with adapalene 0.3%. More patients receiving adapalene were tolerant of the adverse effects compared with tazarotene (55.4% versus 24.4%; $p<0.0012$).

SUMMARY

Professional guidelines recommend topical therapy as standard of care in acne treatment. The American Acne and Rosacea Society guidelines recommend topical benzoyl peroxide, retinoids, and antibiotics as treatments of choice for pediatrics. The updated American Academy of Dermatology guidelines recommend topical retinoids, benzoyl peroxide, and benzoyl peroxide in combination with either erythromycin or clindamycin as effective acne treatments. They also describe the role of specific topical agents in certain subtypes (e.g., dapsone for inflammatory acne, retinoids for comedonal acne, azelaic acid as adjunctive treatment of post inflammatory acne). The Global Alliance to Improve Outcomes in Acne recommends the topical retinoids as the foundation of acne treatment and state that, in general, have similar efficacy, and their efficacy improves with higher concentrations. The concentration and/or vehicle of any particular retinoid may impact tolerability. Combination of a retinoid and antimicrobial such as benzoyl peroxide is the preferred approach for most patients with acne. This combination enhances efficacy and speed of clearing, as the agents target multiple pathophysiological factors and demonstrate broader disease effectiveness. Retinoid monotherapy or combination therapy with benzoyl peroxide should be continued as maintenance treatment due to the potential for bacterial resistance with antibacterials. Topical antibiotics should not be used as monotherapy due to development of resistance.

Also, combination therapy of topical antibiotics and either benzoyl peroxide or topical retinoids is more effective than either agent used alone.

Benzoyl peroxide has bactericidal, keratolytic, and comedolytic activity. It has been useful as a single agent and in combination with antibiotics or retinoids for acne. Combination therapy of benzoyl peroxide with clindamycin or erythromycin is more effective than either of the individual components alone. There are many different strengths and formulations available for benzoyl peroxide. It is unknown if there is increased efficacy from higher or lower concentrations of the products, but the incidence of adverse effects may increase with greater concentrations of drug.

Azelaic acid is an effective agent that possesses comedolytic and antibacterial properties, but the comparative data for efficacy are limited. The combination of sulfur and sodium sulfacetamide is another available agent with keratolytic and antibacterial properties, but there is limited data regarding efficacy.

In July 2016, the FDA approved over-the-counter use of Differin 0.1% gel (adapalene) for the treatment of acne. Differin 0.3% gel still requires a prescription.

In 2019, the FDA approved trifarotene (Aklief), which represents the first new topical retinoid approved for the treatment of acne vulgaris in over 2 decades. It selectively targets retinoic acid receptor (RAR) gamma. Trifarotene is indicated for use in patients 9 years of age and older.

Minocycline topical foam (Amzeeq) is the first topical formulation of minocycline. It offers another topical antibiotic option for the treatment of acne vulgaris in patients 9 years and older.

Clascoterone (Winlevi) was approved in 2020 as the first androgen receptor inhibitor indicated for the treatment of acne vulgaris in male and female patients 12 years of age and older. Clascoterone offers a non-antibiotic, topical option for the management of this condition. Treatment should be withdrawn if hypothalamic pituitary adrenal axis suppression occurs.

REFERENCES

- 1 Differin [package insert]. Fort Worth, TX; Galderma; February 2018.
- 2 Effaclar Gel [package insert]. New York, NY; La Roche-Posay; August 2019.
- 3 Adapalene 0.1%/benzoyl peroxide 2.5% [package insert]. Mahwah, NJ; Glenmark; November 2020.
- 4 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
- 5 Azelex [package insert]. Exton, PA; Almirall. June 2019.
- 6 Acne Medication. [package insert]. Livonia, MI; Rugby; November 2019.
- 7 Advanced Acne Spot Treatment [package insert]. Woonsocket, RI; CVS; December 2014.
- 8 Advanced Acne Wash [package insert]. Vernon Hills, IL; Elorac; July 2015.
- 9 Benzefoam [package insert]. Bridgewater, NJ; Bausch; February 2020.
- 10 Benzepro [package insert]. Scottsdale, AZ; PruGen; rev 1.2.
- 11 BP [package insert]. Dallas, TX; Cintex; June 2012.
- 12 BP Foaming Wash [package insert]. Alpharetta, GA. Acella; December 2009.
- 13 BPO [package insert]. Alpharetta, GA. Acella; July 2018.
- 14 BP Wash [package insert]. Dallas, TX; Cintex; January 2011.
- 15 Cerave Acne Cleanser. Available at : <https://www.cerave.com/skincare/cleansers/acne-benzoyl-peroxide-cleanser>. Accessed January 11, 2022.
- 16 Daylogic Acne Treatment [package insert]. Camp Hill, PA; Rite Aid; October 2011.
- 17 Effaclar Duo [package insert]. New York, NY; La Roche-Posay; August 2019.
- 18 Enzoclear [package insert]. Ocean Springs, MS; Lancer Pharma; July 2019.
- 19 OC8 [package insert]. Ferndale, MI; Ferndale Labs; August 2012.
- 20 Persa-Gel [package insert]. Skillman, NJ; Johnson & Johnson; November 2019.
- 21 Riaux [package insert]. Austin, TX; Artesa Labs; December 2018.
- 22 Acanya [package insert]. Bridgewater, NJ; Valeant; September 2020.
- 23 Benzaclin [package insert]. Bridgewater, NJ; Valeant; February 2017.
- 24 Neuac [package insert]. Fairfield, NJ; Medimetriks; November 2015.
- 25 Onexton [package insert]. Bridgewater, NJ; Bausch; April 2020.

-
- 26 Benzamycin [package insert]. Bridgewater, NJ; Bausch; November 2020.
- 27 Vanoxide-HC [package insert]. Collegeville, PA; Summers. July 2021.
- 28 Winlevi [package insert]. Cranbury, NJ; Sun; September 2021.
- 29 Cleocin T [package insert]. New York, NY; Pfizer; December 2019.
- 30 Clindacin EZT [package insert]. Bronx NY; Perrigo; October 2016.
- 31 Clindacin P [package insert]. Bronx, NJ; Medimetriks; November 2016.
- 32 Clindagel [package insert]. Bridgewater, NJ; Valeant; January 2020.
- 33 Evoclin [package insert]. Morgantown, WV; Mylan; April 2018.
- 34 Aczone [package insert]. Exton, PA; Almirall; August 2021.
- 35 Ery [package insert]. Allegan, MI; Perrigo; August 2011.
- 36 Erygel [package insert]. Morgantown, WV; Mylan; June 2018.
- 37 Amzeeq [package insert]. Bridgewater, NJ; Vyne; January 2021.
- 38 Acne Treatment [package insert]. Woonsocket, RI; CVS; January 2014.
- 39 Advanced Acne Spot Treatment [package insert]. Woonsocket, RI; CVS; December 2014.
- 40 Clearasil Daily Clear [package insert]. Parsippany, NJ; Reckitt Benckiser; September 2011.
- 41 Effaclar Cleanser [package insert]. New York, NY; La Roche-Posay; August 2019.
- 42 Oil-Free Acne Wash [package insert]. Skillman, NJ; Johnson & Johnson; July 2020.
- 43 Rapid Clear [package insert]. Skillman, NJ; Johnson & Johnson; October 2019.
- 44 Effaclar Acne System [package insert]. New York, NY; La Roche-Posay; August 2014.
- 45 Klaron [package insert]. Bridgewater, NJ; Bausch Health; August 2020.
- 46 Ovace [package insert]. San Antonio, TX; Mission; March 2017.
- 47 Ovace Plus Lotion [package insert]. San Antonio, TX; Mission; January 2021.
- 48 Ovace Plus Cream [package insert]. San Antonio, TX; Mission; January 2021.
- 49 Ovace Plus Foam [package insert]. San Antonio, TX; Mission; January 2021.
- 50 Ovace Plus Wash [package insert]. San Antonio, TX; Mission; January 2021.
- 51 Avar [package insert]. San Antonio, TX; Mission; May 2017.
- 52 Avar LS Foam [package insert]. San Antonio, TX; Mission; June 2017.
- 53 Avar E [package insert]. San Antonio, TX; Mission; June 2017.
- 54 Avar E-LS [package insert]. San Antonio, TX; Mission; June 2017.
- 55 Avar LS [package insert]. San Antonio, TX; Mission; June 2017.
- 56 BP 10-1 [package insert]. Alpharetta, GA. Acella; March 2019.
- 57 BP Cleansing Wash [package insert]. Dallas, TX; Cintex; January 2011.
- 58 Plexion [package insert]. Austin, Tx; Artesa Labs; July 2018.
- 59 Rosula [package insert]. Alpharetta, GA. Avion; February 2015.
- 60 SSS 10-5 [package insert]. Scottsdale, AZ; PruGen; November 2020.
- 61 Sulfacleanse [package insert]. Scottsdale, AZ; PruGen; Rev.4.0
- 62 Sumadan [package insert]. Fairfield, NJ; Medimetrick. August 2020.
- 63 Sumaxin [package insert]. Fairfield, NJ; Medimetriks; October 2017.
- 64 Sumaxin TS [package insert]. Fairfield, NJ; Medimetrick. May 2013.
- 65 Palmers Skin Success [package insert]. Englewood Cliffs, NJ; E.T. Browne; November 2021.
- 66 Sulfo Lo [package insert]. Johnson City, TN; Crown; January 2021.
- 67 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
- 68 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
- 69 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
- 70 Tazorac gel [package insert]. Irvine, CA; Allergan; July 2017.
- 71 Altreno [package insert]. Bridgewater, NJ; Valeant; March 2020.
- 72 Atralin [package insert]. Bridgewater, NJ; Valeant; July 2016.
- 73 Avita [package insert]. Morgantown, WC; Mylan; June 2018.
- 74 Refissa [package insert]. Irvine, CA; Zo Skin. June 2018.
- 75 Retin-A [package insert]. Bridgewater, NJ; Valeant; September 2019.
- 76 Retin-A Micro [package insert]. Bridgewater, NJ; Valent; October 2017.
- 77 Twyneo [package insert]. Whippany, NJ; Sol-Gel; July 2021.
- 78 Ziana [package insert]. Bridgewater, NJ; Valeant; March 2017.
- 79 Veltin [package insert]. Exton, PA; Almirall; June 2019.
- 80 Akliel [package insert]. Fort Worth Texas; Galderma; October 2019.
- 81 Rao, J. Acne Vulgaris. Updated August 28, 2020. Available at: <https://emedicine.medscape.com/article/1069804-overview>. Accessed January 11, 2022.
- 82 Lehmann HL, Robinson KA, Andrews JS, et al. Acne therapy: a methodological review. J Am Acad Dermatol. 2002; 47:231-240.
- 83 Titus S, Hodge J. Diagnosis and treatment of acne. Am Fam Physician. 2012; 86(8):734-40.
- 84 Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol. 2003; 49(3 Suppl):S200-210.
- 85 Dreno B. Topical antibacterial therapy for acne vulgaris. Drugs. 2004; 64(21):2389-2397.
- 86 Webster G. Mechanism-based treatment of acne vulgaris: the value of combination therapy. J Drugs Dermatol. 2005; 4(3):281-288.
- 87 Thevarajah S, Balkrishnan R, Camacho FT, et al. Trends in prescription of acne medication in the US: shift from antibiotic to non-antibiotic treatment. J Dermatolog Treat. 2005; 16(4):224-228.
- 88 Eichenfield LF, Krakowski AC, Del Rosso J, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics. 2013;131(3 suppl):S163-86. Available at: https://pediatrics.aappublications.org/content/pediatrics/131/Supplement_3/S163.full.pdf. Accessed January 18, 2022.
-

-
- 89 Zaenglein A, Pathy A, Schlosser B, et al. Guidelines of care for management of acne vulgaris. *J Am Acad Dermatol*. 2016; 74: 943-973. Available at: <https://www.aad.org/member/clinical-quality/guidelines/acne>. Accessed January 18, 2022.
- 90 Thiboutot D, Gollnick H, Dréno, B, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2018; 78(2 suppl): S1-S23. Available at: [https://www.jaad.org/article/S0190-9622\(17\)32603-8/fulltext#sec3.1.1](https://www.jaad.org/article/S0190-9622(17)32603-8/fulltext#sec3.1.1). Accessed January 18, 2022.
- 91 Tanghetti EA, Popp KF. A current review of topical benzoyl peroxide: new perspectives on formulation and utilization. *Dermatol Clin*. 2009; 27(1): 17-24.
- 92 Tanghetti E. The impact and importance of resistance. *Cutis*. 2007; 80(1 Suppl):5-9.
- 93 Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics*. 2006; 118(3):1188-1199.
- 94 Zaenglein AL, Pathy AL, Schlosser BJ, et al for the American Academy of Dermatology. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016; 74(5): 945-973. DOI: 10.1016.j.jaad.2015.12.037. Available at: <https://www.aad.org/member/clinical-quality/guidelines/acne>. Accessed February 1, 2022.
- 95 Titus S, Hodge J. Diagnosis and treatment of acne. *Am Fam Physician*. 2012; 86(8):734-40.
- 96 Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics*. 2006; 118(3):1188-1199.
- 97 Zaenglein AL, Pathy AL, Schlosser BJ. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016; 74(5): 945-973. DOI: 10.1016.j.jaad.2015.12.037. Available at: <https://www.aad.org/member/clinical-quality/guidelines/acne>. Accessed February 1, 2022.
- 98 Zaenglein AL, Pathy AL, Schlosser BJ. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016; 74(5): 945-973. DOI: 10.1016.j.jaad.2015.12.037. Available at: <https://www.aad.org/member/clinical-quality/guidelines/acne>. Accessed February 1, 2022.
- 99 Gupta AK, Nicol K. The use of sulfur in dermatology. *J Drugs Dermatol*. 2004; 3(4):427-31.
- 100 Lin AM, Reimer RJ, Carter DM. Sulfur revisited. *J Am Acad Dermatol*. 1988; 18(3):553-8.
- 101 Aczone [package insert]. Exton, PA; Almirall; August 2021.
- 102 Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics*. 2006; 118(3):1188-1199.
- 103 FDA. Differin approval letter. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2017/020380Orig1s011ltr.pdf. Accessed January 11, 2022.
- 104 Available at: <http://www.clinicalpharmacology-ip.com>. Accessed January 11, 2022.
- 105 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
- 106 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
- 107 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
- 108 Differin [package insert]. Fort Worth, TX; Galderma; February 2018.
- 109 Adapalene 0.1%/benzoyl peroxide 2.5% [package insert]. Mahwah, NJ; Glenmark; November 2020.
- 110 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
- 111 Azelex. [package insert]. Exton, PA; Almirall. June 2019.
- 112 Benzefoam [package insert]. Bridgewater, NJ; Bausch; February 2020.
- 113 Benzefoam Ultra [package insert]. Cumberland, RI; Onset; Rev 0.
- 114 Riax [package insert]. Austin, TX; Artesa Labs; 2013.
- 115 Acanya [package insert]. Bridgewater, NJ; Valeant; September 2020.
- 116 Benzacilin [package insert]. Bridgewater, NJ; Valeant; February 2017.
- 117 Duac [package insert]. Research Triangle Park, NC; Stiefel; April 2015.
- 118 Neucac [package insert]. Fairfield, NJ; Medimetriks; November 2015.
- 119 Onexon [package insert]. Bridgewater, NJ; Bausch; April 2020.
- 120 Aktipak [package insert]. Wayne, PA; Cutanea; January 2017.
- 121 Benzamycin [package insert]. Bridgewater, NJ; Bausch; November 2020.
- 122 Clindagel [package insert]. Bridgewater, NJ; Valeant; January 2020.
- 123 Evoclin [package insert]. Morgantown, WV; Mylan; April 2018.
- 124 Aczone [package insert]. Exton, PA; Almirall; September 2019.
- 125 Erygel [package insert]. Morgantown, WV; Mylan; June 2018.
- 126 Ery [package insert]. Allegan, MI; Perrigo; August 2011.
- 127 Klaron [package insert]. Bridgewater, NJ; Bausch; August 2020.
- 128 Ovace Plus Foam [package insert]. San Antonio, TX; Mission; January 2021.
- 129 Avar Foam [package insert]. San Antonio, TX; Mission; December 2018.
- 130 Plexion [package insert]. Austin, TX; Artesa Labs; July 2018.
- 131 Sumadan [package insert]. Fairfield, NJ; Medimetriks; August 2020.
- 132 Sumaxin [package insert]. Fairfield, NJ; Medimetriks; October 2017.
- 133 Sumaxin TS [package insert]. Fairfield, NJ; Medimetriks. May 2013.
- 134 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
- 135 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
- 136 Tazorac gel [package insert]. Irvine, CA; Allergan; July 2017.
- 137 Altreno [package insert]. Bridgewater, NJ; Valeant; March 2020.
- 138 Atralin [package insert]. Bridgewater, NJ; Valeant; July 2016.
- 139 Avita [package insert]. Morgantown, WV; Mylan; June 2018.
- 140 Retin-A [package insert]. Bridgewater, NJ; Valeant; September 2019.
- 141 Retin-A Micro [package insert]. Bridgewater, NJ; Valeant; October 2017.
- 142 Ziana [package insert]. Bridgewater, NJ; Valeant; March 2017.
- 143 Veltin [package insert]. Exton, PA; Almirall; June 2019.
- 144 Cleocin T [package insert]. New York, NY; Pfizer; November 2017.
- 145 Amzeeq [package insert]. Bridgewater, NJ; Vyne; January 2021.
-

146 Akliel [package insert]. Fortworth, TX; Galderma; October 2019.
147 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
148 Winlevi [package insert]. Cranbury, NJ; Sun; September 2021.
149 Twynéo [package insert]. Whippany, NJ; Sol-Gel; July 2021.
150 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
151 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
152 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
153 Differin [package insert]. Fort Worth, TX; Galderma; February 2018.
154 Adapalene 0.1%/benzoyl peroxide 2.5% [package insert]. Mahwah, NJ; Glenmark; November 2020.
155 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
156 Azelex. [package insert]. Exton, PA; Almirall. June 2019.
157 Benzefoam [package insert]. Bridgewater, NJ; Bausch; February 2020.
158 Benzefoam Ultra [package insert]. Cumberland, RI; Onset; Rev 0.
159 Riax [package insert]. Austin, TX; Artesa Labs; 2013.
160 Acanya [package insert]. Bridgewater, NJ; Valeant; September 2020.
161 Benzaclin [package insert]. Bridgewater, NJ; Valeant; February 2017.
162 Duac [package insert]. Research Triangle Park, NC; Stiefel; April 2015.
163 Neuac [package insert]. Fairfield, NJ; Medimetriks; November 2015.
164 Onexton [package insert]. Bridgewater, NJ; Valeant; October 2016.
165 Aktipak [package insert]. Wayne, PA; Cutanea; January 2017.
166 Benzamycin [package insert]. Bridgewater, NJ; Bausch; November 2020.
167 Clindagel [package insert]. Bridgewater, NJ; Valeant; January 2020.
168 Evoclin [package insert]. Morgantown, WV; Mylan; April 2018.
169 Aczone [package insert]. Exton, PA; Almirall; August 2021.
170 Erygel [package insert]. Morgantown, WV; Mylan; June 2018.
171 Ery [package insert]. Allegan, MI; Perrigo; August 2011.
172 Klaron [package insert]. Bridgewater, NJ; Bausch; August 2020.
173 Ovace Plus Foam [package insert]. San Antonio, TX; Mission; January 2021.
174 Avar Foam [package insert]. San Antonio, TX; Mission; December 2018.
175 Plexion [package insert]. Austin, TX; Artesa Labs; July 2018.
176 Sumadan [package insert]. Fairfield, NJ; Medimetriks; August 2020.
177 Sumaxin [package insert]. Fairfield, NJ; Medimetriks. October 2017.
178 Sumaxin TS [package insert]. Fairfield, NJ; Medimetriks. May 2013.
179 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
180 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
181 Tazorac gel [package insert]. Irvine, CA; Allergan; July 2017.
182 Altreno [package insert]. Bridgewater, NJ; Valeant; March 2020.
183 Atralin [package insert]. Bridgewater, NJ; Valeant; July 2016.
184 Avita [package insert]. Morgantown, WC; Mylan; June 2018.
185 Retin-A [package insert]. Bridgewater, NJ; Valeant; September 2019.
186 Retin-A Micro [package insert]. Bridgewater, NJ; Valent; October 2017.
187 Ziana [package insert]. Bridgewater, NJ; Valeant; March 2017.
188 Veltin [package insert]. Exton, PA; Almirall; June 2019.
189 Cleocin T [package insert]. New York, NY; Pfizer; November 2017.
190 Amzeeq [package insert]. Bridgewater, NJ; Foamix; October 2019.
191 Akliel [package insert]. Fortworth, TX; Galderma; October 2019.
192 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
193 Twynéo [package insert]. Whippany, NJ; Sol-Gel; July 2021.
194 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
195 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
196 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
197 Differin [package insert]. Fort Worth, TX; Galderma; February 2018.
198 Adapalene 0.1%/benzoyl peroxide 2.5% [package insert]. Mahwah, NJ; Glenmark; November 2020.
199 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
200 Azelex. [package insert]. Exton, PA; Almirall. June 2019.
201 Benzefoam [package insert]. Bridgewater, NJ; Bausch; February 2020.
202 Benzefoam Ultra [package insert]. Cumberland, RI; Onset; Rev 0.
203 Riax [package insert]. Austin, TX; Artesa Labs; 2013.
204 Acanya [package insert]. Bridgewater, NJ; Valeant; September 2020.
205 Benzaclin [package insert]. Bridgewater, NJ; Valeant; February 2017.
206 Duac [package insert]. Research Triangle Park, NC; Stiefel; April 2015.
207 Neuac [package insert]. Fairfield, NJ; Medimetriks; November 2015.
208 Onexton [package insert]. Bridgewater, NJ; Bausch; April 2020.
209 Aktipak [package insert]. Wayne, PA; Cutanea; January 2017.
210 Benzamycin [package insert]. Bridgewater, NJ; Bausch; November 2020.

211 Clindagel [package insert]. Bridgewater, NJ; Valeant; January 2020.
212 Evoclin [package insert]. Morgantown, WV; Mylan; April 2018.
213 Aczone [package insert]. Exton, PA; Almirall; September 2019.
214 Erygel [package insert]. Morgantown, WV; Mylan; June 2018.
215 Ery [package insert]. Allegan, MI; Perrigo; August 2011.
216 Klaron [package insert]. Bridgewater, NJ; Bausch; August 2020.
217 Ovace Plus Foam [package insert]. San Antonio, TX; Mission; January 2021.
218 Avar Foam [package insert]. San Antonio, TX; Mission; December 2018.
219 Plexion [package insert]. Austin, Tx; Artesa Labs; July 2018.
220 Sumadan [package insert]. Fairfield, NJ; Medimetriks; August 2020.
221 Sumaxin [package insert]. Fairfield, NJ; Medimetriks; October 2017.
222 Sumaxin TS [package insert]. Fairfield, NJ; Medimetriks; May 2013.
223 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
224 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
225 Tazorac gel [package insert]. Irvine, CA; Allergan; July 2017.
226 Atralin [package insert]. Bridgewater, NJ; Valeant; July 2016.
227 Avita [package insert]. Morgantown, WC; Mylan; January 2018.
228 Retin-A [package insert]. Bridgewater, NJ; Valeant; September 2019.
229 Retin-A Micro [package insert]. Bridgewater, NJ; Valent; October 2017.
230 Ziana [package insert]. Bridgewater, NJ; Valeant; March 2017.
231 Veltin [package insert]. Exton, PA; Almirall; June 2019.
232 Cleocin T [package insert]. New York, NY; Pfizer; November 2017.
233 Amzeeq [package insert]. Bridgewater, NJ; Vyne; January 2021.
234 Akliel [package insert]. Fortworth, TX; Galderma; October 2019.
235 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
236 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
237 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018
238 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
239 Differin [package insert]. Fort Worth, TX; Galderma; April 2018.
240 Adapalene 0.1%/benzoyl peroxide 2.5% [package insert]. Mahwah, NJ; Glenmark; November 2020.
241 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
242 Azelex. [package insert]. Exton, PA; Almirall. June 2019.
243 Benzefoam [package insert]. Bridgewater, NJ; Bausch; February 2020.
244 Benzefoam Ultra [package insert]. Cumberland, RI; Onset; Rev 0.
245 Riax [package insert]. Austin, TX; Artesa Labs; 2013.
246 Acanya [package insert]. Bridgewater, NJ; Valeant; September 2020.
247 Benzacilin [package insert]. Bridgewater, NJ; Valeant; February 2017.
248 Duac [package insert]. Research Triangle Park, NC; Stiefel; April 2015.
249 Neuac [package insert]. Fairfield, NJ; Medimetriks; November 2015.
250 Onexton [package insert]. Bridgewater, NJ; Bausch; April 2020.
251 Aktipak [package insert]. Wayne, PA; Cutanea; January 2017.
252 Benzamycin [package insert]. Bridgewater, NJ; Bausch; November 2020
253 Clindagel [package insert]. Bridgewater, NJ; Valeant; January 2020.
254 Evoclin [package insert]. Morgantown, WV; Mylan; April 2018.
255 Aczone [package insert]. Exton, PA; Almirall; August 2021.
256 Erygel [package insert]. Morgantown, WV; Mylan; June 2018.
257 Ery [package insert]. Allegan, MI; Perrigo; August 2011.
258 Klaron [package insert]. Bridgewater, NJ; Bausch; August 2020.
259 Ovace Plus Foam [package insert]. San Antonio, TX; Mission; January 2021.
260 Avar Foam [package insert]. San Antonio, TX; Mission; December 2018.
261 Plexion [package insert]. Austin, Tx; Artesa Labs; July 2018.
262 Sumadan [package insert]. Fairfield, NJ; Medimetriks; August 2020.
263 Sumaxin [package insert]. Fairfield, NJ; Medimetriks; October 2017.
264 Sumaxin TS [package insert]. Fairfield, NJ; Medimetriks; May 2013.
265 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
266 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
267 Tazorac gel [package insert]. Irvine, CA; Allergan; July 2017.
268 Altreno [package insert]. Bridgewater, NJ; Valeant; March 2020.
269 Atralin [package insert]. Bridgewater, NJ; Valeant; July 2016.
270 Avita [package insert]. Morgantown, WC; Mylan; June 2018.
271 Retin-A [package insert]. Bridgewater, NJ; Valeant; September 2019.
272 Retin-A Micro [package insert]. Bridgewater, NJ; Valent; October 2017.
273 Ziana [package insert]. Bridgewater, NJ; Valeant; March 2017.
274 Veltin [package insert]. Exton, PA; Almirall; June 2019.
275 Cleocin T [package insert]. New York, NY; Pfizer; November 2017.

276 Amzeeq [package insert]. Bridgewater, NJ; Vyne; January 2021.
277 Akliel [package insert]. Fort Worth Texas; Galderma; October 2019.
278 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
279 Twyneo [package insert]. Whippany, NJ; Sol-Gel; July 2021.
280 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
281 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
282 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
283 Differin [package insert]. Fort Worth, TX; Galderma; April 2018.
284 Adapalene 0.1%/benzoyl peroxide 2.5% [package insert]. Mahwah, NJ; Glenmark; November 2020.
285 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
286 Azelex. [package insert]. Exton, PA; Almirall. June 2019.
287 Benzefoam [package insert]. Bridgewater, NJ; Bausch; February 2020.
288 Benzefoam Ultra [package insert]. Cumberland, RI; Onset; Rev 0.
289 Riax [package insert]. Austin, TX; Artesa Labs; 2013.
290 Acanya [package insert]. Bridgewater, NJ; Valeant; September 2020.
291 Benzaclin [package insert]. Bridgewater, NJ; Valeant; February 2017.
292 Duac [package insert]. Research Triangle Park, NC; Stiefel; April 2015.
293 Neuac [package insert]. Fairfield, NJ; Medimetriks; November 2015.
294 Onexton [package insert]. Bridgewater, NJ; Bausch; April 2020.
295 Aktipak [package insert]. Wayne, PA; Cutanea; January 2017.
296 Benzamycin [package insert]. Bridgewater, NJ; Bausch; November 2020.
297 Clindagel [package insert]. Bridgewater, NJ; Valeant; January 2020.
298 Evoclin [package insert]. Morgantown, WV; Mylan; April 2018.
299 Aczone [package insert]. Exton, PA; Almirall; August 2021.
300 Erygel [package insert]. Morgantown, WV; Mylan; June 2018.
301 Ery [package insert]. Allegan, MI; Perrigo; August 2011.
302 Klaron [package insert]. Bridgewater, NJ; Bausch; August 2020.
303 Ovace Plus Foam [package insert]. San Antonio, TX; Mission; January 2021.
304 Avar Foam [package insert]. San Antonio, TX; Mission; December 2018.
305 Plexion [package insert]. Austin, TX; Artesa Labs; July 2018.
306 Sumadan [package insert]. Fairfield, NJ; Medimetriks; August 2020.
307 Sumaxin [package insert]. Fairfield, NJ; Medimetriks; October 2017.
308 Sumaxin TS [package insert]. Fairfield, NJ; Medimetriks; May 2013.
309 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.
310 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.
311 Tazorac gel [package insert]. Irvine, CA; Allergan; July 2017.
312 Altreno [package insert]. Bridgewater, NJ; Valeant; March 2020.
313 Atralin [package insert]. Bridgewater, NJ; Valeant; July 2016.
314 Avita [package insert]. Morgantown, WC; Mylan; June 2018.
315 Retin-A [package insert]. Bridgewater, NJ; Valeant; September 2019.
316 Retin-A Micro [package insert]. Bridgewater, NJ; Valent; October 2017.
317 Ziana [package insert]. Bridgewater, NJ; Valeant; March 2017.
318 Veltin [package insert]. Exton, PA; Almirall; June 2019.
319 Cleocin T [package insert]. New York, NY; Pfizer; November 2017.
320 Amzeeq [package insert]. Bridgewater, NJ; Vyne; January 2021.
321 Akliel [package insert]. Fort Worth Texas; Galderma; October 2019.
322 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.
323 Onexton. Available at: <https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2201>. Accessed January 11, 2022.
324 Winlevi [package insert]. Cranbury, NJ; September 2021.
325 Twyneo [package insert]. Whippany, NJ; Sol-Gel; July 2021.
326 Piette WW, Taylor S, Pariser D, et al. Hematologic safety of dapsone gel, 5%, for topical treatment of acne vulgaris. Arch Dermatol. 2008; 144(12):1564-70.
327 Differin [package insert]. Fort Worth, TX; Galderma; February 2018.
328 Plixda [package insert]. Charleston, SC; Marnel; August 2018.
329 Epiduo [package insert]. Fort Worth, TX; Galderma; February 2018
330 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
331 Azelex. [package insert]. Exton, PA; Almirall. June 2019.
332 Differin [package insert]. Fort Worth, TX; Galderma; April 2018.
333 Adapalene 0.1%/benzoyl peroxide 2.5% [package insert]. Mahwah, NJ; Glenmark; November 2020.
334 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.
335 Azelex. [package insert]. Exton, PA; Almirall. June 2019.
336 Benzefoam [package insert]. Bridgewater, NJ; Bausch; February 2020.
337 Benzefoam Ultra [package insert]. Cumberland, RI; Onset; Rev 0.
338 Riax [package insert]. Austin, TX; Artesa Labs; 2013.

339 Acanya [package insert]. Bridgewater, NJ; Valeant; September 2020.

340 Benzaclin [package insert]. Bridgewater, NJ; Valeant; February 2017.

341 Duac [package insert]. Research Triangle Park, NC; Stiefel; April 2015.

342 Neuac [package insert]. Fairfield, NJ; Medimetriks; November 2015.

343 Onexton [package insert]. Bridgewater, NJ; Bausch; April 2020.

344 Aktipak [package insert]. Wayne, PA; Cutanea; January 2017.

345 Benzamycin [package insert]. Bridgewater, NJ; Bausch; November 2020.

346 Clindagel [package insert]. Bridgewater, NJ; Valeant; January 2020.

347 Evoclin [package insert]. Morgantown, WV; Mylan; April 2018.

348 Aczone [package insert]. Exton, PA; Almirall; September 2019.

349 Erygel [package insert]. Morgantown, WV; Mylan; June 2018.

350 Ery [package insert]. Allegan, MI; Perrigo; August 2011.

351 Klaron [package insert]. Bridgewater, NJ; Bausch; August 2020.

352 Ovace Plus Foam [package insert]. San Antonio, TX; Mission; January 2021.

353 Avar Foam [package insert]. San Antonio, TX; Mission; December 2018.

354 Plexion [package insert]. Austin, Tx; Artesa Labs; July 2018.

355 Sumadan [package insert]. Fairfield, NJ; Medimetriks; August 2020.

356 Sumaxin [package insert]. Fairfield, NJ; Medimetriks; October 2017.

357 Sumaxin [package insert]. Fairfield, NJ; Medimetriks; May 2013.

358 Palmers Skin Success [package insert]. Englewood Cliffs, NJ; E.T. Browne; November 2021.

359 Sulfo-Lo [package insert]. Johnson City, TN; Crown; May 2019.

360 Fabior foam [package insert]. Greenville, NC; Mayne; June 2018.

361 Tazorac cream [package insert]. Irvine, CA; Allergan; July 2017.

362 Tazorac gel [package insert]. Irvine, CA; Allergan; July 2017.

363 Altreno [package insert]. Bridgewater, NJ; Valeant; March 2020.

364 Atralin [package insert]. Bridgewater, NJ; Valeant; July 2016.

365 Avita [package insert]. Morgantown, WC; Mylan; June 2018.

366 Retin-A [package insert]. Bridgewater, NJ; Valeant; September 2019.

367 Retin-A Micro [package insert]. Bridgewater, NJ; Valent; October 2017.

368 Ziana [package insert]. Bridgewater, NJ; Valeant; March 2017.

369 Veltin [package insert]. Exton, PA; Almirall; June 2019.

370 Cleocin T [package insert]. New York, NY; Pfizer; November 2017.

371 Amzeeq [package insert]. Bridgewater, NJ; Vyne; January 2021.

372 Akliel [package insert]. Fortworth, TX; Galderma; October 2019.

373 Daylogic Acne Treatment [package insert]. Camp Hill, PA; Rite Aid; October 2011.

374 Enzoclear [package insert]. Ocean Springs, MS; Lancer Pharma; July 2019.

375 Arazlo [package insert]. Bridgewater, NJ; Bausch; May 2021.

376 Effaclar Cleanser [package insert]. New York, NY; La Roche-Posay; August 2019.

377 Effaclar Acne System [package insert]. New York, NY; La Roche-Posay; August 2014.

378 Cerave Acne Cleanser. Available at : <https://www.cerave.com/skincare/cleansers/acne-benzoyl-peroxide-cleanser>. Accessed January 11, 2022.

379 Twyneo [package insert]. Whippany, NJ; Sol-Gel; July 2021.

380 Del Rosso, JQ. Study results of benzoyl peroxide 5%/clindamycin 1% topical gel, adapalene 0.1% gel, and use in combination for acne vulgaris. *Journal of Drugs in Dermatology*. 2007; 6(6):616-622.

381 Leyden J, Lowe N, Kakita L, et al. Comparison of treatment of acne vulgaris with alternate-day applications of tazarotene 0.1% gel and once-daily applications of adapalene 0.1% gel: a randomized trial. *Cutis*. 2001; 67(6 Suppl):10-16.

382 Webster GF, Guenther L, Poulin YP, et al. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. *Cutis*. 2002; 69(2 Suppl):4-11.

383 Cunliffe WJ, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and U.S. multicenter trials. *J Am Acad Dermatol*. 1997; 36(6 Pt 2):S126-134.

384 Cunliffe WJ, Danby FW, Dunlap F, et al. Randomized, controlled trial of the efficacy and safety of adapalene gel 0.1% and tretinoin cream 0.05% in patients with acne vulgaris. *Eur J Dermatol*. 2002; 12(4):350-354.

385 Thiboutot D, Gold MH, Jarratt MT, et al. Randomized controlled trial of the tolerability, safety, and efficacy of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. *Cutis*. 2001; 68(4 Suppl):10-19.

386 Grosshans E, Marks R, Mascaro JM, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. *Br J Dermatol*. 1998; 139(Suppl 52):26-33.

387 Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol*. 1996; 34(3):482-485.

388 Thiboutot DM, Weiss J, Bucko A, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. *J Am Acad Dermatol*. 2007; 57(5):791-9.

389 Gold LS, Tran J, Cruz-Santana A, et al. Adapalene-BPO Study Group. A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. *Cutis*. 2009; 84(2):110-116.

390 Epiduo Forte [package insert]. Fort Worth, TX; Galderma; October 2021.

391 Neuac [package insert]. Fairfield, NJ; Medimetriks; November 2018.

392 Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: Assessment of efficacy and safety in 2813 patients. *J Am Acad Dermatol*. 2008; 59(5):792-800.

-
- 393 Webster G, Rich P, Gold MH, et al. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and low concentration benzoyl peroxide (2.5%) aqueous gel in moderate or severe acne subpopulations. *J Drugs Dermatol*. 2009; 8(8):736-743.
- 394 Leyden JJ, Hickman JG, Jarratt MT, et al. The efficacy and safety of a combination benzoyl peroxide/clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination product. *J Cutan Med Surg*. 2001; 5(1):37-42.
- 395 Leyden JJ, Berger RS, Dunlap FE, et al. Comparison of the efficacy and safety of a combination topical gel formulation of benzoyl peroxide and clindamycin with benzoyl peroxide, clindamycin and vehicle gel in the treatments of acne vulgaris. *Am J Clin Dermatol*. 2001; 2(1):33-39.
- 396 Tschen EH, Katz HI, Jones TM, et al. A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. *Cutis*. 2001; 67(2):165-169.
- 397 Zhang JZ, Li LF, Tu YT, et al. A successful maintenance approach in inflammatory acne with adapalene gel 0.1% after an initial treatment in combination with clindamycin topical solution 1% or after monotherapy with clindamycin topical solution 1%. *J Dermatolog Treat*. 2004; 15(6):372-378.
- 398 Wolf JE Jr, Kaplan D, Kraus SJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. *J Am Acad Dermatol*. 2003; 49(3 Suppl):S211-217.
- 399 Jarrett M, Brundage T. Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: a randomized, double-blind, vehicle-controlled study. *J Drugs in Dermatol*. 2012; 11(3):318-326.
- 400 Fleischer AB Jr, Shalita A, Eichenfield LF, et al. Dapsone gel combination treatment study group. Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4% or moisturizer for the treatment of acne vulgaris: a 12-week, randomized, double-blind study. *J Drugs Dermatol*. 2010; 9(1):33-40.
- 401 Kircik L. Community-based trial results of combination clindamycin 1%-benzoyl peroxide 5% topical gel plus tretinoin microsphere gel 0.04% or 0.1% or adapalene gel 0.1% in the treatment of moderate to severe acne. *Cutis*. 2007; 80(suppl 1):10-14.
- 402 Leyden JJ, Shalita AR, Saatjian GD, et al. Erythromycin 2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. *J Am Acad Dermatol*. 1987; 16(4):822-827.
- 403 Draeos ZD, Tanghetti EA. Tazarotene Combination Leads to Efficacious Acne Results (CLEAR) Trial Study Group. Optimizing the use of tazarotene for the treatment of facial acne vulgaris through combination therapy. *Cutis*. 2002; 69(2 Suppl):20-29.
- 404 Tanghetti E, Dhawan S, et al. Tazarotene 0.1 percent cream plus clindamycin 1 percent gel versus tretinoin 0.025 percent gel plus clindamycin 1 percent gel in the treatment of facial acne vulgaris. *Dermatol Online J*. 2007;13(3):1.
- 405 Leyden JJ, Tanghetti EA, Miller B, et al. Once-daily tazarotene 0.1 % gel versus once-daily tretinoin 0.1 % microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. *Cutis*. 2002; 69(2 Suppl):12-19.
- 406 Webster GF, Berson D, Stein LF, et al. Efficacy and tolerability of once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.025% gel in the treatment of facial acne vulgaris: a randomized trial. *Cutis*. 2001; 67(6 Suppl):4-9.
- 407 Kircik LH. Tretinoin microsphere gel pump 0.04% versus tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne vulgaris. *J Drugs Dermatol*. 2009; 8(7):650-654.
- 408 Seidler EM, Kimball AB. Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne. *J Am Acad Dermatol*. 2010; 63(1):52-62.
- 409 Kolli SS, Pecone D, Pona A, et al. Topical retinoids in acne vulgaris: a systemic review. *Am J Clin Dermatol*. 2019; 20(3):345-365. DOI: 10.1007/s40257-019-00423-z.