

Therapeutic Class Overview

Acne Agents

INTRODUCTION

- Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules (*Zaenglein et al 2016*). Four primary pathogenic factors interact in a complex manner to produce the different acne lesions. The four factors include sebum production by the sebaceous gland, Propionibacterium acnes (*P. acnes*) follicular colonization, alteration in the keratinization process, and the release of inflammatory mediators to the skin (*Thiboutot et al 2009*).
- Several options exist for the treatment of acne vulgaris including topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, laser and light therapies, miscellaneous therapies, complementary and alternative therapies, and dietary restrictions. Topical therapy of acne vulgaris includes agents that are available over the counter or by prescription, and choice of therapy can be influenced by various factors including patient age, site of involvement, extent and severity of disease, and patient preference. Topical agents include antibiotics, benzoyl peroxide, retinoids, azelaic acid, dapson, salicylic acid, and clascoterone, a topical androgen inhibitor approved by the Food and Drug Administration (FDA) in August 2020. (*Gollnick et al 2016, Zaenglein et al 2016, FDA summary [Winlevi] 2020*).
- Traditionally, the treatment of acne vulgaris has been directed toward controlling *P. acnes* and centered on the use of antibiotics. Current treatment modalities are directed toward as many pathogenic factors as possible. Combination treatment has the ability to target multiple pathogenic factors, including inflammatory and noninflammatory lesions (*Eichenfield et al 2013, Thiboutot et al 2009*). Data have shown that combination therapy results in faster and more complete clearing of acne vulgaris lesions compared with monotherapy (*Eichenfield et al 2013, Nast et al 2016, Thiboutot et al 2009*). Combination therapy should be used in the majority of patients with acne (*Gollnick et al 2016, Zaenglein et al 2016*). Additionally, antibiotics and benzoyl peroxide both target *P. acnes*; however, unlike antibiotics, benzoyl peroxide has not been associated with the development of bacterial resistance (*Zaenglein et al 2016*). The exact mechanism of clascoterone is unknown; the postulated mechanism is competition against dihydrotestosterone for binding to androgen receptors within the sebaceous gland and hair follicles (*Winlevi prescribing information 2020, Cassiopea press release 2019*).
- Topical retinoids are recommended as monotherapy in primarily mild, comedonal acne, or in combination with topical or oral antibiotics in patients with mixed or primarily inflammatory moderate acne vulgaris (*Gollnick et al 2016, Zaenglein et al 2016*). The comedolytic and anti-comedogenic properties associated with topical retinoids result in a reduction in the formation of microcomedones and comedones (*Zaenglein et al 2016*). For severe acne, oral antibiotics with topical therapy or oral isotretinoin is recommended for first-line treatment (*Zaenglein et al 2016, Zaenglein et al 2018*). Oral isotretinoin is one of several alternatives for treatment-resistant moderate acne. Clascoterone was primarily studied in patients with moderate to severe acne (*Hebert et al 2020*).
- The focus of this review will be the use of the topical agents and oral isotretinoin for the treatment of acne. Agents prescribed solely for rosacea and products combining hyaluronate, niacinamide, cholestyramine, or resorcinol will not be included in this review. The following table may not be all inclusive as products enter and leave the market frequently in this class.
- Medispan Class: Acne Products

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Antibiotics	
Aczone (dapson) gel 5%, 7.5%	✓
Cleocin-T (clindamycin) lotion 1%	✓
Clindacin-P, Clindacin ETZ (clindamycin) swab 1%	✓
Clindacin Pac, Clindacin ETZ (clindamycin and cleanser kit) swab 1%	✓
Clindagel (clindamycin) gel 1%	✓
clindamycin solution 1%	✓

Drug	Generic Availability
Evoclin (clindamycin) foam 1%	✓
NuCaraClinPAK (clindamycin and moisturizer kit) gel 1%	✓
Ery (erythromycin) pads 2%	■
Erygel (erythromycin) gel 2%	✓
erythromycin solution 2%	✓
Amzeeq (minocycline) topical foam 4%	-
Benzoyl Peroxide and Combinations	
benzoyl peroxide bar 10%; cream 2.5%, 10%; cleanser 3.5% ; cleanser ER 4.4%; external liquid 2.5%, 4%, 5%, 5.5%, 6%, 6.9%, 7%, 10%; foam 5.3%, 9.8%, 10%; gel 2.5%, 4%, 5%, 6.5%, 8%, 10%; foaming cloths 6%; lotion 5%, 8%, 10%; wash/lotion kits 2.5/3.7%, 2.5/10%	✓ †
Enzoclear, BenzePrO (benzoyl peroxide) foam 9.8%	✓ *
Riax (benzoyl peroxide) foam 5.5%, 9.5%	-
BenzePrO, BPO (benzoyl peroxide) foam 5.2%, 9.7%; external liquid 6.8%; foaming cloths 5.8%	-
Zaclir (benzoyl peroxide) lotion 8%	-
Vanoxide-HC (benzoyl peroxide/hydrocortisone) lotion 5/0.5%	✓ *
benzoyl peroxide/hydrocortisone lotion 7.5/1%	✓ *
Inova kit (benzoyl peroxide/vitamin E) pad/topical 4/5%, 8/5%	■ *
Inova 4/1, 8/2 kit (benzoyl peroxide/salicylic acid/vitamin E) pad/pad/topical 4/1/5%, 8/2/5%	■ *
Benzoyl Peroxide – Antibiotic Combinations	
Acanya (benzoyl peroxide/clindamycin) gel 2.5/1.2%	✓
BenzaClin (benzoyl peroxide/clindamycin) gel 5/1%	✓
Neuac (benzoyl peroxide/clindamycin) gel, kit 5/1.2%	✓
NuCaraRxPAK (benzoyl peroxide/clindamycin) kit 2.5/1%	✓
Onexton (benzoyl peroxide/clindamycin) gel 3.75/1.2%	-
Benzamycin (benzoyl peroxide/erythromycin) gel 5/3%	✓
Topical Retinoids – Single Entity	
adapalene external solution 0.1%, pad 0.1%	✓
Differin (adapalene) cream 0.1%; gel 0.1% [†] , 0.3%	✓
Differin (adapalene) lotion 0.1%	-
Arazlo (tazarotene) lotion 0.045%	-
Fabior (tazarotene) foam 0.1%	✓ ■
Tazorac (tazarotene) gel and cream 0.05%, gel 0.1%	-
Tazorac (tazarotene) cream 0.1%	✓
Altreno (tretinoin) lotion 0.05%	-
Atralin (tretinoin) gel 0.05%	✓
Avita (tretinoin) cream 0.025%	✓
Avita (tretinoin) gel 0.025%	■ ■
Retin-A (tretinoin) cream 0.025%, 0.05%, 0.1%; gel 0.01%, 0.025%	✓
Retin-A Micro (tretinoin microsphere) gel 0.04%, 0.1%	✓
Retin-A Micro (tretinoin microsphere) gel 0.06%, 0.08%	-
Aklief (trifarotene) cream 0.005%	-
Topical Retinoids – Combination	

Drug	Generic Availability
Epiduo (adapalene/benzoyl peroxide) gel 0.1/2.5%	✓
Epiduo Forte (adapalene/benzoyl peroxide) gel 0.3/2.5%	-
Adainzde (adapalene/benzoyl peroxide/clindamycin) gel 0.3/2.5/1%	✓
Veltin, Ziana (clindamycin phosphate/tretinoin) gel 1.2/0.025%	✓
Miscellaneous Topical Therapies	
Azelex (azelaic acid) cream 20%	-
Sulfacetamide/Sulfur and Combinations	
sodium sulfacetamide cream 10% (Ovace Plus); lotion 9.8% (Ovace Plus), 10% (Klaron); shampoo 10% (Ovace Plus); wash external liquid 10% (Ovace, Ovace Plus); wash external gel 10% (Ovace Plus); foam 9.8% (Ovace Plus)	✓
sulfacetamide with sulfur wash 9/4% (Sumaxin), 9/4.5% (Sumadan); with sulfur cleanser 9.8/4.8% (Plexion), 10/2% (Avar LS); with sulfur emulsion 10/1% (BP 10-1, Sulfamez), 10/5% (Avar); with sulfur in urea emulsion 10/4% , 10/5%; with sulfur suspension 8/4% (SulfaCleanse), 9/4.5% (Clenia Plus) , 10/5%; with sulfur cream 9.8/4.8% (Plexion), 10/2% (Avar-e LS), 10/5% (Avar-e Emollient, Avar-e Green, SSS 10-5); with sulfur foam 10/5% (SSS 10-5); with sulfur lotion 9.8/4.8% (Plexion), 10/5%; with sulfur pad 10/4% (Sumaxin); with sulfur cloths 9.8/4.8% (Plexion)	✓
Sumadan kit wash 9/4.5%, Sumaxin CP kit pad 10/4%, (sulfacetamide sodium/sulfur/skin cleanser)	✓*
Sumadan XLT kit wash 9/4.5% (sulfacetamide sodium/sulfur/sunscreen)	✓*
sulfur external bar 3% , 10%; lotion 5%	✓*
SASTid (sulfur/salicylic acid) external bar 3/5%	✓*
sulfacetamide sodium/salicylic acid external suspension 8/2%, 10/5%	✓*
Oral Retinoids	
Absorica (isotretinoin) oral capsule 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg	- †
Absorica LD (isotretinoin) oral capsule 8 mg, 16 mg, 24 mg, 32 mg	-
Accutane , Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin) oral capsule 10 mg, 20 mg, 30 mg, 40 mg	✓ §
Androgen Receptor Inhibitor	
Winlevi (clascoterone) cream 1%	-

Abbreviation: ER = extended-release

*Over-the-counter (OTC) only product(s)

†Prescription and/or OTC product(s)

‡Absorica 10, 20, 30, and 40 mg products are BX rated according to the Orange Book, considered to be not therapeutically equivalent to other pharmaceutically equivalent products;

§Claravis is the reference standard and other products are branded generics considered bioequivalent to Claravis

|| **Avita 0.025% gel is BT rated, considered to be not therapeutically equivalent to other pharmaceutically equivalent products.**

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications*

Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Antibiotics					
Aczone (dapsone)	✓	-	-	-	-
Clindamycin	✓	-	-	-	-

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Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Erythromycin	✓	-	-	-	-
Amzeeq (minocycline)	✓	-	-	-	-
Benzoyl Peroxide – Single Entity					
Benzoyl peroxide	✓	-	-	✓	-
Benzoyl Peroxide – Antibiotic Combinations					
Benzoyl peroxide/clindamycin	✓ (Acanya, Benzaclin, Onexton)	✓ (Neuac)	-	-	-
Benzoyl peroxide/erythromycin	✓ (Benzamycin)	-	-	-	-
Benzoyl Peroxide – Other Combinations					
Vanoxide-HC (benzoyl peroxide/hydrocortisone)	✓	-	-	-	-
Topical Retinoids – Single Entity					
Differin (adapalene)	✓	-	-	-	-
Arazlo, Fabior, Tazorac (tazarotene) [†]	✓ (0.1% Tazorac strengths only)	-	-	-	-
Tretinoin	✓	-	-	-	-
Aklief (trifarotene)	✓	-	-	-	-
Topical Retinoids – Combination					
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	✓	-	-	-	-
Veltin, Ziana (clindamycin/tretinoin)	✓	-	-	-	-
Miscellaneous Topical Therapies					
Azelex (azelaic acid)	-	✓	-	-	-
Sulfacetamide/Sulfur and Combinations					
Sulfacetamide	✓ (gel, lotion)	-	-	-	-
Sulfacetamide/sulfur	-	-	✓	-	-
Oral Retinoids					
Absorica, Absorica LD, Accutane, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	-	-	-	-	✓
Androgen Receptor Inhibitor					
Winlevi (clascoterone)	✓	-	-	-	-

Note: OTC only products are not listed

*Approved ages vary by product.

[†]Tazorac is also approved for the treatment of psoriasis.

(Prescribing information: Absorica/Absorica LD 2020, Acanya 2020, Accutane 2010, Aczone 7.5% 2019, Aczone 5% 2018, adapalene topical solution 2020, adapalene/benzoyl peroxide/clindamycin gel 2020, Aklief 2019, Altreno 2020, Amnesteem 2018, Amzeeq 2019, Arazlo 2019, Atralin 2016, Azelex 2019, Benzaclin 2017, Benzamycin 2020, benzoyl peroxide/salicylic acid 2020, BPO 4% gel 2018, Claravis 2018, Cleocin T 2019, Clenia Plus 2021, Clindagel 2017, Differin cream 2011, Differin lotion 2018, Duac 2015, Epiduo 2018, Epiduo Forte 2015, Fabior 2018, Myorisan 2019, Onexton 2020, Retin-A 2019, Retin-A Micro 2017, sodium sulfacetamide monohydrate/salicylic acid 2019, SulfaCleanse 2017, Tazorac gel 2019, Tazorac cream 2019, Vanoxide-HC 2018, Veltin 2019, Winlevi 2020, Zenatane 2019, Ziana 2017, Clinical Pharmacology 2021, Lexi-comp 2021, Micromedex 2021)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- All agents included in this review are FDA-approved for the treatment of acne vulgaris, and clinical trials have demonstrated their effectiveness compared to a placebo vehicle. In addition, there have been some trials evaluating the comparative efficacy of the agents in the class. This clinical efficacy summary will focus on comparative trials.

Dapsone

- Dapsone was shown to be effective in the management of acne. In a clinical trial comparing dapsone 5% gel to the combination of dapsone plus adapalene, dapsone plus benzoyl peroxide, or dapsone plus moisturizer, all treatment arms showed similar efficacy in reducing inflammatory lesions over 12 weeks (*Fleischer et al 2010*).
- The approval of dapsone 7.5% gel was based on 2 randomized, double-blind (DB), vehicle-controlled, multicenter (MC) studies. A total of 4,340 patients were randomized to receive dapsone 7.5% gel or vehicle once daily for 12 weeks. The primary endpoint was the percentage of patients with none (score of 0) or minimal (score of 1) on the 5-point Global Acne Assessment Score (GAAS) scale at week 12. The key secondary endpoints were mean absolute change from baseline in both inflammatory and non-inflammatory lesion counts (*Eichenfield et al 2016, Stein et al 2016*).
 - The majority of the subjects had moderate acne vulgaris, ie, 20 to 50 inflammatory and 30 to 100 non-inflammatory lesions at baseline.
 - In both studies, the GAAS success rate was approximately 30% in the dapsone arm and 21% in the vehicle arm.
 - In Study 1, the mean percent reduction in inflammatory lesions was 55.5% in the dapsone group and 49% in the vehicle group. In Study 2, it was 53.8% and 47.3%, respectively.
 - For the mean percent reduction in non-inflammatory lesions, 44.4% was reported in the dapsone group and 38.4% in the vehicle group in Study 1. In Study 2, it was 45.9% in the dapsone group and 40.4% in the vehicle group.

Benzoyl Peroxide

- There is limited evidence that differentiates the various formulations (gels, lotions, solutions, etc.) and strengths of the benzoyl peroxide and antibiotic combination agents. Clinical studies evaluating combination therapy with benzoyl peroxide and either clindamycin or erythromycin have consistently demonstrated that these agents are more effective compared to their respective monotherapies (*Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Lookingbill et al 1997, Thiboutot et al 2008b, Webster et al 2009, Xu et al 2016*).
- In a study by Leyden et al (n = 492), patients with moderate to severe acne vulgaris were randomized to receive benzoyl peroxide/clindamycin, benzoyl peroxide/erythromycin, or benzoyl peroxide alone for 10 weeks. The decrease in the number of inflammatory lesions from baseline, the primary endpoint, was significantly greater for those treated with benzoyl peroxide/clindamycin compared to benzoyl peroxide alone (p = 0.04). The average decrease in the number of inflammatory lesions was similar in patients treated with benzoyl peroxide/clindamycin and benzoyl peroxide/erythromycin (p = 0.4) (*Leyden et al 2001*).
- In a meta-analysis by *Seidler et al*, there was a significantly greater percent reduction in noninflammatory acne lesion count with benzoyl peroxide/clindamycin 2.5%/1.2% (-43.4%; 95% confidence interval [CI] depicted but not reported) compared to benzoyl peroxide/clindamycin 5%/1% (-38.2%; 95% CI depicted but not reported), benzoyl peroxide alone (-34.2%; 95% CI depicted but not reported), clindamycin alone (-27.9%; 95% CI depicted but not reported) and placebo (-14.9%; 95% CI depicted but not reported) over 10 to 12 weeks of treatment (*Seidler et al 2011*).
- Three clinical trials comparing benzoyl peroxide/clindamycin to adapalene monotherapy have reported consistently that the combination of benzoyl peroxide/clindamycin significantly reduces total lesion count over 12 weeks compared to adapalene (*Langner et al 2008, Ko et al 2009*). The combination of benzoyl peroxide/clindamycin in two trials also significantly reduced inflammatory lesion counts compared to baseline at week 12 to a greater extent than adapalene (*Langner et al 2008, Ko et al 2009*). For non-inflammatory lesion count, there were conflicting results among the studies (*Guerra-Tapia et al 2012, Ko et al 2009, Langner et al 2008*).

Topical Retinoids

- Several comparative studies have been conducted evaluating the topical retinoids. Efficacy results are mixed, with trials demonstrating:

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- Equivalent efficacy between tretinoin 0.04% microgel and tretinoin 0.1% microgel (*Berger et al 2007*)
- Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.025% gel (*Cunliffe et al 1997, Ellis et al 1998, Grosshans et al 1998*)
- Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.1% microgel (*Nyirady et al 2001*)
- Equivalent efficacy between adapalene 0.1% gel and tazarotene 0.1% cream (*Pariser et al 2008*)
- Equivalent efficacy between adapalene 0.3% gel and tazarotene 0.1% gel (*Thiboutot et al 2008a*)
- Greater efficacy with tazarotene 0.1% plus clindamycin 1% gel over adapalene 0.1% plus clindamycin 1% gel (*Maiti et al 2017*).
- Greater efficacy with tazarotene 0.1% cream over adapalene 0.3% gel (*Tanghetti et al 2010*)
- Greater efficacy with tazarotene 0.1% cream over adapalene 0.1% cream (*Shalita et al 2005*)
- Greater efficacy with tretinoin 0.05% gel over adapalene 0.1% gel (*Pierard-Franchimont et al 1999*)
- Greater efficacy with adapalene 0.1% gel over tretinoin 0.025% gel (*Cunliffe et al 1997, Shalita et al 1996*)
- Two studies (n = 820 for each study) demonstrated that tretinoin 0.05% lotion was more effective than a vehicle in improving Evaluator's Global Severity Score (EGSS) and reducing the number of inflammatory and non-inflammatory facial lesions at week 12 in patients aged ≥ 9 years (all $p < 0.001$). Success rates were 9.6% higher in Study 1 and 7.3% higher in Study 2 compared to the vehicle (*Tyring et al 2018*).
- Two studies (n = 1614 total) found that tazarotene 0.045% lotion significantly improved EGSS and the number of inflammatory and non-inflammatory lesions compared to vehicle in patients aged ≥ 9 years with moderate to severe acne. Success rates were 12.3% to 12.5% higher compared to vehicle in Study 1 and 2, respectively (*Arazlo prescribing information 2019*).
- Two randomized studies (n = 2420 total) found that patients aged ≥ 9 years with moderate acne experienced greater improvement in Investigator's Global Assessment (IGA) of the face and the number of inflammatory and non-inflammatory lesions (all $p < 0.001$) with trifarotene 0.005% cream compared to vehicle (*Tan et al 2019*).
- A meta-analysis of 5 MC, investigator-blinded, randomized controlled trials (RCTs) compared the efficacy of adapalene 0.1% gel to tretinoin 0.025% gel in the treatment of patients with acne vulgaris (n = 900) (*Cunliffe et al 1998*). Overall, adapalene demonstrated equivalent efficacy to tretinoin in terms of reducing inflammatory lesions ($p = 0.51$), non-inflammatory lesions ($p = 0.38$), and total lesion count ($p = 0.48$) at week 12, but demonstrated more rapid efficacy in reducing inflammatory and total lesions at week 1 compared to tretinoin ($p < 0.05$).
- A systematic review of 54 clinical trials compared the efficacy and safety/tolerability of the topical retinoids for the treatment of acne vulgaris:
 - Of 5 studies that compared use of adapalene to tazarotene, 4 found no difference in the percent change of the total lesion count between the two treatments. One study, which combined both adapalene and tazarotene with clindamycin, found a significant change in lesion count with tazarotene plus clindamycin (17.54 vs 11.03; $p = 0.007$).
 - In one study comparing adapalene 0.3%, 0.1% to tretinoin 0.05%, a significantly greater reduction in total lesion count was found with tretinoin at week 12 (76.7% tretinoin vs 66.4% adapalene 0.3% vs 57.8% adapalene 0.1%; $p < 0.001$).
 - In a 12-week study of 40 patients, no difference in efficacy was found between tretinoin and tazarotene in the change in IGA, absolute change in inflammatory and noninflammatory lesion count, and total lesion count from baseline to week 12.
 - When comparing safety, 62% of patients receiving tretinoin 0.05% reported adverse effects (AE), compared to 19% and 40% with adapalene 0.1% and 0.3%, respectively. Treatment with tazarotene was associated with significantly more AE than treatment with adapalene (55.4 vs 24.4%; $p < 0.0012$) (*Kolli et al 2019*).
- A retrospective, investigator-blinded, vehicle-controlled, photographic assessment study was conducted to assess the efficacy of topical retinoids as monotherapy for the treatment of inflammatory acne (*Leyden et al 2005*). Five investigators rated pre- and post-treatment photographs of patients (n = 577) who had participated in 12- or 15-week, DB, RCTs of tazarotene 0.1% gel, adapalene 0.1% gel, tretinoin 0.1% microgel, tretinoin 0.025% gel, and tazarotene 0.1% cream.
 - Tazarotene, adapalene, and tretinoin were all superior to vehicle. Between-retinoid comparisons showed greater incidences of clinically significant improvements in overall acne severity in the tazarotene group compared with the groups receiving adapalene ($p \leq 0.001$) or tretinoin ($p \leq 0.01$).
- There are several limitations to these studies, including relatively small sample sizes (range, n = 25 to 323), short duration (typically 12 weeks), enrollment of patients with varying degrees of acne severity, and comparisons between different strengths and formulations of topical retinoids. In addition, most studies that showed greater efficacy data with adapalene were sponsored by Galderma, greater efficacy data with tretinoin were sponsored by Johnson and Johnson

(Ortho Dermatologics), and greater efficacy data with tazarotene were sponsored by Allergan. Based on the varying efficacy results and study limitations, it is not clear whether one topical retinoid is more effective than another.

- Tazarotene foam led to greater decreases from baseline for all types of acne lesions compared to vehicle foam; direct comparisons to other forms of tazarotene and other therapies have not been completed (*Fabior prescribing information, 2018, Feldman et al 2013*).
- For the combination products, several studies evaluated the effectiveness of the combination products compared to their individual components. The adapalene/benzoyl peroxide combination showed a statistically superior success rate compared to monotherapy with adapalene or benzoyl peroxide (*Gold et al 2009, Gollnick et al 2009, Pariser et al 2007, Thiboutot et al 2007*). In addition, the clindamycin/tretinoin combination had statistically significant superiority for all comparisons vs monotherapy with clindamycin or tretinoin (*Jarratt et al 2012, Leyden et al 2006, Schlessinger et al 2007*).

Oral retinoids

- A 2018 Cochrane review evaluated 31 RCTs of oral isotretinoin to assess its efficacy and safety for acne vulgaris. Included trials were comparisons to placebo, systemic antibiotics plus topical agents (combination therapy), or isotretinoin in various formulations or dose regimens (*Costa et al 2018*). For the primary outcome of total inflammatory lesion count, oral isotretinoin did not produce a greater reduction in acne lesions compared to combination therapy after 20 to 24 weeks of therapy in patients with moderate to severe acne (risk ratio [RR], 1.01; 95% CI, 0.96 to 1.06; n=3 studies; 400 patients). Another primary outcome of serious adverse effect frequency detected 1 serious event of Stevens-Johnson syndrome in the isotretinoin group. The risk of serious adverse effects was higher with oral isotretinoin compared to combination therapy but was not considered statistically significant (RR, 3.0; 95% CI, 0.12 to 72.98). Less serious adverse effects were significantly higher with isotretinoin compared to combination therapy (RR, 1.67; 95% CI, 1.42 to 1.98; n = 2 studies; 351 patients). Oral isotretinoin compared to oral isotretinoin plus topical agents did not demonstrate a significant difference in outcomes. For dose regimens, continuous low dose and conventional isotretinoin dose demonstrated a greater decrease in inflammatory lesion count compared to intermittent dosing (1 week each month). Due to study design limitations, the authors of the review rated the level of this evidence as low to very low.

Androgen receptor inhibitor

- In 2 RCTs in patients (n = 1440) aged ≥ 9 years with moderate to severe facial acne, clascoterone cream (n = 709) was associated with significantly higher treatment success compared with vehicle cream (n = 712). Three coprimary endpoints were evaluated: treatment success (a 2-point reduction in IGA compared to baseline and a score of clear or almost clear), absolute change from baseline noninflammatory lesion count, and inflammatory lesion count at week 12. Patients treated with clascoterone cream achieved IGA success vs vehicle cream (Study 1: 18.4 vs 8.7%; difference, 10.1%; 95% CI, 4.1 to 16%; Study 2: 20.9 vs 6.6%; difference, 14.3%; 95% CI, 8.9 to 19.7%) at week 12. There was a significant reduction in absolute noninflammatory lesions from baseline to -20.4 and -19.5 with clascoterone treatment compared with -13 and -10.8 with vehicle in Study 1 and 2, respectively. A significant reduction in inflammatory lesions from baseline to -19.3 and -20.1 vs -15.4 and -12.6 with vehicle in Study 1 and 2, respectively. Adverse event rates were low and mostly mild, mainly trace or mild erythema (*Hebert et al 2020, Winlevi prescribing information 2020*).
 - An open-label, 9-month extension study evaluated the safety of clascoterone (n = 317) vs vehicle (n = 290) in 607 patients. Adverse events occurred in 18.3% of clascoterone patients and 17.9% of vehicle patients. The most frequent treatment-emergent adverse events (TEAEs) with clascoterone were nasopharyngitis, upper respiratory infection, sinusitis and application site acne. A total of 2.8% of clascoterone-treated patients experienced a TEAE that led to discontinuation (swelling, dryness and acne at the application site, mild polycystic ovaries, moderate hair color changes, and severe suicide attempt) vs no patients treated with the vehicle (*Eichenfeld et al 2020*).

Other products

- No pertinent clinical studies were recently identified for the treatment of acne vulgaris with sulfacetamide or azelaic acid as monotherapy. Both are FDA-approved for the treatment of acne vulgaris.

CLINICAL GUIDELINES

- The American Academy of Dermatology (AAD) 2016 guidelines, the 2016 European evidence-based recommendations, and a 2018 consensus from the Global Alliance to Improve Outcomes in Acne generally suggest the use of combinations to treat acne (*Nast et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*). The 2016 AAD Guidelines

recommend retinoids as monotherapy in primarily comedonal acne, or in combination with topical or oral antibiotics in patients with mixed or primarily inflammatory acne lesions. Topical antibiotics are noted as effective therapies for acne; however, they are not recommended as monotherapy due to the risk of resistance. Benzoyl peroxide or combinations with antibiotics (erythromycin or clindamycin) are effective treatments as well and are recommended as monotherapy for mild acne, or with a topical retinoid or systemic antibiotic therapy for moderate to severe acne. Oral isotretinoin is one of the recommended treatment options for severe nodular acne and moderate acne that is treatment resistant or that causes scarring or psychosocial distress. Azelaic acid (Azelex) is a useful adjunctive therapy per the AAD and topical dapsone 5% gel can be recommended for inflammatory acne, particularly in adult females (*Zaenglein et al 2016*, *Thiboutot et al 2018*).

- A 2016 consensus-based guideline for the treatment of acne recommends that patients with predominant comedonal acne should initially be treated with a topical retinoid (preferred), azelaic acid, or salicylic acid. For patients with predominant papulopustular acne, fixed combination topicals are recommended, and should be used along with oral antibiotics, oral isotretinoin, oral zinc, or oral anti-androgenic hormonal therapy (women only) for patients with moderate to severe disease. For nodular/conglobate acne, treatment should include monotherapy with oral isotretinoin, or fixed combination topicals plus oral antibiotics for men; for women, these options may be supplemented with oral anti-androgenic hormonal therapy. To prevent the disease from recurring, maintenance therapy with a topical retinoid (preferred) or azelaic acid is recommended once a patient is clear or almost clear of their acne (*Gollnick et al 2016*).
- The 2013 recommendations from the American Acne and Rosacea Society (endorsed by the American Academy of Pediatrics) state that acne management of pediatric patients is similar to acne treatment in older adolescents and adults. For mild acne, benzoyl peroxide, a topical retinoid, or a combination of benzoyl peroxide with an antibiotic or retinoid is recommended. For moderate and severe acne, combination topical therapy with the possible addition of oral antibiotics may be considered. Oral isotretinoin may be considered for some patients with severe, refractory, and scarring acne (*Eichenfield et al 2013*).
- Androgen receptor inhibitors, like clascoterone, have yet to be incorporated into treatment guidelines.

SAFETY SUMMARY

- Oral isotretinoin carries a black box warning regarding its teratogenicity risk; therefore, its use is contraindicated in female patients who are or may become pregnant. If pregnancy does occur during treatment, the drug should be discontinued and the patient should be referred to a specialist in reproductive toxicity. The drug is available only through a restricted program call the iPLEDGE program, which requires enrollment by prescribers, patients, pharmacies, and distributors. The restricted program has very specific requirements regarding use of contraception if the drug is used in females with reproductive potential.
- Contraindications for the acne agents are primarily hypersensitivity to any component of the product. For clindamycin-containing products, clindamycin is contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Tazarotene (Arazlo, Fabior, Tazorac) is contraindicated in pregnant women.
- Warnings for antibiotics include the risk for superinfection and pseudomembranous colitis. Gels contain alcohol and may be flammable; use caution. Benzoyl peroxide-containing products may cause bleaching of fabric or hair; use care when applying. Retinoids and benzoyl peroxide-containing products may cause ultraviolet (UV) sensitivity; avoid exposure or limit exposure with sunscreen. Retinoids may cause local application site reactions such as erythema, scaling, and dryness especially for the first few weeks of use. Altreno and Atralin product labels recommend caution in patients with a fish allergy due to the potential for allergenicity to fish protein. Azelaic acid products may cause hypopigmentation, and can irritate the eyes and mucous membranes. Dapsone gel can cause methemoglobinemia resulting in hospitalization, particularly in patients with glucose-6 phosphate dehydrogenase deficiency or idiopathic methemoglobinemia.
- Warnings for oral isotretinoin include avoidance of micro-dosed progesterone preparations as contraception, risk of psychiatric disorders (depression, psychosis, suicidal behavior/thoughts), pseudotumor cerebri, Stevens-Johnson syndrome, acute pancreatitis, lipid abnormalities, hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities, ocular abnormalities, and glucose and creatine phosphokinase abnormalities.
- Warnings for topical clascoterone include hypothalamic-pituitary-adrenal (HPA) axis suppression, greater susceptibility to systemic toxicity in pediatric patients, and hyperkalemia.
- Adverse events for topical acne agents are generally limited to local application site reactions including burning/stinging, erythema, scaling, and dryness.
- Common adverse reactions of oral isotretinoin include dryness in skin, lips, and eyes; arthralgia; headache; dermatitis; musculoskeletal discomfort; reduced visual acuity; and upper respiratory symptoms/infection.

- Avoid concurrent use of clindamycin with erythromycin due to possible antagonistic therapeutic effects based on *in vitro* data.
- In June 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use.
 - The OTC topical acne products of concern are marketed under various brand names such as Proactiv, Neutrogena, MaxClarity, Oxy, Ambi, Aveeno, Clean & Clear, and as store brands. They are available as gels, lotions, face washes, solutions, cleansing pads, toners, face scrubs, and other products.
 - Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both. The FDA is continuing to monitor and evaluate this safety issue, and will work with manufacturers regarding any future label changes that would address the risk of severe hypersensitivity reactions. The hypersensitivity reactions may occur within minutes to a day or longer after product use. These serious hypersensitivity reactions differ from the local skin irritation that may occur at the product application site, such as redness, burning, dryness, itching, peeling, or slight swelling, that are already included in the Drug Facts labels. (*Clinical Pharmacology 2021*, *FDA Drug Safety Communication 2014*, *Micromedex 2021*)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Antibiotics				
Aczone (dapsones)	Gel	Topical	Apply once (7.5% dose) to twice daily (5% dose).	If no improvement in 12 weeks, treatment should be reassessed. The 7.5% gel is indicated in age ≥ 9 years. The 5% gel is indicated in age ≥ 12 years.
Clindagel, Cleocin T, Clindacin-P, Clindacin ETZ, Clindacin Pac, Evoclin, NuCaraClinPAK (clindamycin)	Foam, gel, lotion, solution, swab, swab + cleanser kit, gel kit	Topical	Foam and gel (Clindagel): Apply once daily. Gel (Cleocin T), lotion, solution, or swab: Apply twice daily.	If topical antibiotic therapy is longer than a few weeks, the addition of topical benzoyl peroxide is recommended. Indicated in age ≥ 12 years.
Erygel, Ery (erythromycin)	Gel, pads, solution	Topical	Apply once to twice daily.	If no improvement after 6 to 8 weeks, or if the condition worsens, discontinue treatment. If topical antibiotic therapy is longer than a few weeks, the addition of topical benzoyl peroxide is recommended.
Amzeeq (minocycline)	Foam	Topical	Apply once daily.	Indicated in age ≥ 9 years.
Benzoyl Peroxide and Combinations				
BenzePrO, BPO, Benziq LS, Enzoclear, Riax, Zaclir (benzoyl peroxide)	Bar, cream, cleanser ER, external liquid, foam, gel, foaming cloths, lotion, wash + lotion kits	Topical	Cream, foam, gel, solution, lotion: Apply once daily.	Improvement is usually noted in 3 to 4 weeks.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Foaming cloths, lotion, cleanser, bar, wash, liquid: Apply 1 to 3 times daily.	
Vanoxide-HC (benzoyl peroxide/hydrocortisone)	Lotion	Topical	Apply 1 to 3 times daily.	Product expires 3 months after dispensed.
Inova (benzoyl peroxide/vitamin E)	Pad/topical kit	Topical	As directed.	
Inova 4/1, 8/2 kit (benzoyl peroxide/salicylic acid/vitamin E)	Pad/pad/topical kit	Topical	As directed.	
Benzoyl Peroxide – Antibiotic Combinations				
Acanya, Benzacilin, Neuc, NuCaraRxPAK, Onexton (benzoyl peroxide/clindamycin)	Gel, gel kit	Topical	Benzacilin: Apply twice daily. All other products: Apply once daily in the evening.	Indicated in age ≥ 12 years.
Benzamycin (benzoyl peroxide/erythromycin)	Gel	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Topical Retinoids – Single Entity				
Differin (adapalene)	Cream, gel, lotion, external solution, pad	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Arazlo, Fabior, Tazorac (tazarotene)	Foam, gel, cream, lotion	Topical	Apply once daily in the evening.	Efficacy has not been established past 12 weeks. Indicated in age ≥ 12 years. Arazlo is indicated in age ≥ 9 years.
Altreno, Atralin, Avita, Retin-A, Retin-A Micro (tretinoin)	Lotion, cream, gel, microsphere gel	Topical	Apply once daily.	Altreno is indicated in age ≥ 9 years, Atralin is indicated in age ≥ 10 years, and all other products in age ≥ 12 years.
Aklief (trifarotene)	Cream	Topical	Apply once daily in the evening.	Indicated in age ≥ 9 years.
Topical Retinoids - Combination				
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	Gel	Topical	Apply once daily.	Epiduo is indicated in age ≥ 9 years and Epiduo Forte in age ≥ 12 years.
Adainzde (adapalene/benzoyl peroxide/clindamycin)	Gel	Topical	Apply once daily.	
Veltin, Ziana (clindamycin/tretinoin)	Gel	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Miscellaneous Topical Therapies				
Azelex (azelaic acid)	Cream	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Sulfacetamide/Sulfur and Combinations				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Klaron, Ovace, Ovace Plus (sulfacetamide) Avar, Avar LS, Avar-e LS, Avar-e Emollient, Avar-e Green, BP 10-1, Clenia Plus , Plexion, SSS 10-5, SulfaCleanse , Sulfamez, Sumadan, Sumadan XLT, Sumaxin, Sumaxin CP (sulfacetamide/sulfur)	Monotherapy: Cream, foam, wash external gel, lotion, shampoo, wash external liquid With sulfur: cleanser, cloths, cream, emulsion, foam, gel, lotion, pad, suspension, wash Kits with sulfur: wash + cleanser, pad + cleanser, wash + sunscreen	Topical	Foam, cleanser cream, lotion, gel, bar, wash, kits: Apply 1 to 3 times daily.	Indicated in age \geq 12 years.
Sulfur SASTid (sulfur/salicylic acid)	Bar, lotion (sulfur only)	Topical	Apply 1 to 3 times daily.	
sulfacetamide sodium/salicylic acid	External suspension	Topical	Apply as directed by physician	
Oral Retinoids				
Absorica, Absorica LD, Accutane , Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	Capsule	Oral	Accutane , Amnesteem, Claravis, Myorisan, Zenatane: Twice daily with food. Absorica, Absorica LD: Twice daily with or without food.	Once daily dosing is not recommended. Duration of treatment: 15 to 20 weeks Pregnancy tests should be performed before prescribing, each month during therapy, and 1 month after discontinuation. Baseline lipids and liver function tests should be performed. Absorica and Absorica LD are indicated in age \geq 12 years. The other oral isotretinoin products have not been studied in children < 12 years of age.
Androgen Receptor Inhibitor				
Winlevi (clascoterone)	Cream	Topical	Twice daily	Indicated in age \geq 12 years.

Abbreviation: ER = extended release

See the current prescribing information for full details

(**Clinical Pharmacology 2021, Lexi-comp 2021**)

CONCLUSION

- Current treatment of acne vulgaris is primarily topical agents. Guidelines suggest the use of combinations to treat acne (*Eichenfield et al 2013, Nast et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*).
- Dapsone (Aczone), clindamycin, erythromycin, and minocycline (Amzeeq) are topical antibiotics for the treatment of acne vulgaris. Most agents have formulations available as generics (minocycline is brand-only). Antibiotics have a slow onset of action and may pose an increased risk for bacterial resistance. Antibiotics should be used in combination therapy if used for more than a few weeks (*Eichenfield et al 2013, Thiboutot et al 2009*).
- Topical benzoyl peroxide, available OTC, is often used for initial self-treatment of acne (*Medical Letter 2020*). Various dosage formulations and strengths are available. Benzoyl peroxide is used in combination with other topical agents for acne. Excessive drying may occur with benzoyl peroxide use and may be observed as marked peeling, erythema, possible edema, and allergic contact sensitization. Additionally, benzoyl peroxide may bleach hair and/or fabric so care must be used to limit accidental exposure (*Lexi-comp 2021*). In 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use. Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both (*FDA Drug Safety Communication 2014*).
- Topical retinoids, including adapalene (Differin), tazarotene (Arazlo, Fabior, Tazorac), tretinoin (Retin-A, Altreno, Atralin, Avita), and Aklief (trifarotene) are effective in the treatment of acne vulgaris. Combinations of topical retinoids include adapalene/benzoyl peroxide (Epiduo, Epiduo Forte) and clindamycin/tretinoin (Veltin, Ziana). In studies comparing the agents, no one agent was consistently more efficacious than another, and combination agents demonstrated greater efficacy when compared to monotherapy with their components. Guidelines do not recommend one retinoid over another (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*). A topical retinoid, alone or in combination with benzoyl peroxide and/or a topic antibiotic, is often used for first-line treatment of inflammatory and noninflammatory acne (*Medical Letter 2020*). Retinoid/antimicrobial combinations are more effective than either component alone, especially in patients with inflammatory acne. All topical retinoids normalize keratinization and appear to have anti-inflammatory effects.
- Most of the adverse reactions associated with retinoids are dermatological and may lessen with continued use. Retinoids cause increased sun sensitivity, and their use should be avoided with other agents that cause excessive drying. Differin gel is now available as an OTC product.
- The topical benzoyl peroxide and antibiotic combination products include benzoyl peroxide/clindamycin (Acanya, Benzacilin, Duac, Neuac, and Onexton) and benzoyl peroxide/erythromycin (Benzamycin). The benzoyl peroxide/clindamycin products primarily differ in their respective strengths. Acanya contains 2.5% benzoyl peroxide and 1.2% clindamycin, Benzacilin contains 5% benzoyl peroxide and 1% clindamycin, Duac and Neuac contain 5% benzoyl peroxide and 1.2% clindamycin, and Onexton contains 3.75% benzoyl peroxide and 1.2% clindamycin. The benzoyl peroxide and antibiotic combination agents are effective for the treatment of acne vulgaris. Combination treatment with benzoyl peroxide and either clindamycin or erythromycin has been shown to be more effective than treatment with each individual agent alone (*Lookingbill et al 1997, Webster et al 2009, Thiboutot et al 2008, Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Xu et al 2016*). Current clinical guidelines support the use of combination treatment in order to limit the development of bacterial resistance (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*).
- Oral isotretinoin is a recommended treatment option for severe nodular acne and treatment-resistant moderate acne. (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*). Isotretinoin has also been considered the most effective medication for treatment of inflammatory acne (*Medical Letter 2020*). Its efficacy was not found to be better than the combination of a systemic antibiotic with a topical agent (*Costa et al 2018*). It is available only through a restricted distribution program due to its teratogenic effects. If used in female patients, appropriate contraception is required. Additionally, the agent is associated with several other adverse events that require monitoring.
- Two other treatment options are sulfacetamide and azelaic acid (Azelex). Sulfacetamide is available in a variety of dosage forms and strengths and in combination with sulfur. Azelaic acid, a branded agent, is another topical treatment option for acne and is recommended by the guidelines for both mild acne as monotherapy and for moderate acne in combination with another class of topical acne agents (*Nast et al 2016, Gollnick et al 2016, Zaenglein et al 2016*).
- An androgen receptor inhibitor, clascoterone, is a newer treatment for acne with a unique mechanism of action. Phase 3 RCTs have demonstrated its superiority in efficacy over a vehicle cream (*Hebert et al 2020*). Common adverse events

are application site reactions and nasal/respiratory symptoms (*Eichenfeld et al 2020, Hebert et al 2020, Winlevi prescribing information 2020*).

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Publication Date: April 2, 2021