

Drug Class Review: Severe Acne

Date of Review: November 2018

End Date of Literature Search: 08/28/2018

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Review:

To evaluate evidence for medications used in the treatment of severe cystic acne as requested by the Health Evidence Review Commission (HERC). In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, acne has historically been an unfunded condition with the exception of acne conglobata.¹ However, as of January 1, 2019, acne fulminans will be a covered condition, and as of January 1, 2020, severe cystic acne will also be a covered condition.²

Research Questions:

1. What is the comparative efficacy and effectiveness of treatments for severe acne (topical agents such as adapalene, adapalene/benzoyl peroxide, tretinoin, tazarotene, benzoyl peroxide, salicylic acid, dapsone, azelaic acid, clindamycin, erythromycin, sulfacetamide; oral systemic antibiotics such as doxycycline, minocycline, tetracycline, azithromycin, erythromycin, clindamycin, trimethoprim, and sulfamethoxazole/trimethoprim; hormonal agents such as oral contraceptives and spironolactone; and oral isotretinoin)?
2. What are the comparative harms of treatments for severe acne?
3. Are there subpopulations of patients in which a particular treatment for severe acne would be more effective or associated with less harm?

Conclusions:

- This drug class review is limited by the lack of high quality evidence from high quality systematic reviews and guidelines which evaluate the comparative efficacy and safety of treatments for severe acne. There are also limited randomized controlled trials in the severe acne population and the majority of the trials are older with methodological and conflict of interest concerns.
- There is insufficient evidence to determine comparative efficacy and safety of treatments for severe acne.
- There is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for severe acne.
- Though not of high methodological quality due to conflict of interest concerns, recent guidelines from the American Academy of Dermatology, European Academy of Dermatology and Venereology, and American Academy of Pediatrics recommend multiple treatment options for severe acne, all including isotretinoin.³⁻⁵ Other recommended treatments include combination therapy with systemic antibiotics and topical therapies such as benzoyl peroxide, retinoids, or topical antibiotics.³⁻⁵ Recommendations for treatment of mild to moderate acne generally includes the same therapies, either as monotherapy or in differing combinations, but isotretinoin is generally not recommended until acne is severe.³⁻⁵
- Isotretinoin has substantial safety concerns compared to other medications for acne.⁶ There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin. Because of the teratogenicity risk, it is approved for marketing only under a REMS program called iPLEDGE™.⁶

Recommendations:

- Implement prior authorization (PA) criteria for the Acne preferred drug list (PDL) class, which contains federal legend topical medications that have an FDA-approved and OHA-funded indication for severe acne vulgaris as well as oral isotretinoin, to limit use to funded conditions (**Appendix 5**).
- Designate at least one formulation of the following medications/classes as a preferred agent on the PDL due to guideline support for use in severe acne: oral isotretinoin, topical benzoyl peroxide, topical retinoid (adapalene or tretinoin), and topical antibiotics.
- After evaluation of comparative costs in executive session, make all single source brand agents non-preferred and all other agents in the Acne PDL class preferred.

Background:

Acne is a chronic inflammatory disease of the skin which affects approximately 50 million patients in the United States and around 85% of patients 12-24 years of age.^{7,8} Acne may also persist into adulthood.^{5,9} Pathogenic factors include androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles by *Propionibacterium acnes*.¹⁰ Pathogenesis may also be influenced by family history, diet, and other factors.^{5,7,10} Acne is characterized by seborrhea, non-inflammatory and inflammatory lesions, and scarring and is commonly located on the face (majority of cases), neck, chest, and back.¹⁰ Acne, particularly severe acne, may result in permanent scarring and psychological morbidity such as poor self-esteem, depression, and anxiety.^{5,11}

There is currently no universal acne classification system, but acne is commonly classified as mild, moderate, or severe.⁵ Assessment tools may include factors such as type of acne, number of lesions, anatomic location, quality of life, and scarring.⁵ A consensus statement from the Journal of the American Academy of Dermatology in 1990 defines severe acne as the presence of any of the following: persistent or recurrent inflammatory nodules, extensive papulopustular disease, ongoing scarring, persistent purulent and/or serosanguineous drainage from lesions, or presence of sinus tracks.¹² Moderate-to-severe acne is thought to affect around 20% of young patients.⁷ Acne conglobata and acne fulminans are two forms of severe acne. Acne conglobata is a severe form of nodular acne which involves recurrent abscesses and communicating sinuses.¹³ Acne fulminans is a severe variant of inflammatory acne characterized by an explosive onset of painful erosions and hemorrhagic crusts that lead to severe and often disfiguring scars.¹⁴ Systemic systems such as fever and arthralgias may also be present with acne fulminans.^{13,14}

Treatment for acne may include a variety of agents such as topical medications (i.e. retinoids, benzoyl peroxide, topical antibiotics, salicylic acid, azelaic acid, sulfacetamide), systemic antibiotics (i.e. doxycycline, minocycline, erythromycin, azithromycin, clindamycin, trimethoprim), hormonal agents (i.e. oral contraceptives, spironolactone, antiandrogens), and oral isotretinoin.³⁻⁵ Choice of treatment depends on severity of disease, with isotretinoin specifically FDA-approved for severe recalcitrant nodular acne and recommended for severe acne.³⁻⁶ Other treatments for severe acne usually include combination therapy with multiple classes of medications which can also be used for mild or moderate acne.³⁻⁵ Recent guidelines for acne are discussed in detail later in this review. These classes of medications are well-established and all have been FDA-approved for many years. Isotretinoin was initially approved in 1982.⁶ Selected medications with FDA-approved indications or common off-label use for acne are further described in **Table 1**.

Clinically meaningful outcomes for acne assessment include quality of life and symptom reduction as demonstrated by lesion counts or acne severity. Though there seems to be no universally determined minimal clinically important difference for these outcomes, a consensus view of the authors of the European Evidence-Based Guidelines for Treatment of Acne suggested a minimal clinically important difference of 10% greater reduction in number of lesions for a treatment to demonstrate superior efficacy.⁴

In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, acne has historically been an unfunded condition with the exception of acne conglobata.¹ However, as of January 1, 2019, acne fulminans will be a covered condition and as of January 1, 2020, severe cystic acne will also be a covered condition.^{2,15} In the OHP FFS population, there are approximately 7,598 patients with a diagnosis of acne vulgaris (L70.0) and 56 patients with a diagnosis of acne conglobata (L70.1), the only severe form of acne with its own ICD-10 code.

Current OHP FFS policy management (beyond PDL status) of medications which can be used for acne (**Table 1**) includes the following:

- Oral tetracyclines: quantity limit of two 14 day supplies in a 3 month timeframe; PA required to ensure FDA-approved and OHP-funded diagnosis for requests over the quantity limit
- Topical tazarotene cream and gel: PA is required. The PA is focused on psoriasis and atopic dermatitis indications, but requests for acne would require that the diagnosis is funded by OHP.

A summary of relevant drug information for topical agents and isotretinoin (which make up the Acne PDL class) is available in **Appendix 2**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Acne Indications and Dosing^{6,16}

Drug Name (Brand Name)	Acne Indication: FDA-Approved or Off-Label?	Acne Formulations	Acne Dosing
TOPICAL AGENTS			
Adapalene (Differin)	FDA-approved for acne	<ul style="list-style-type: none"> • Cream • Gel • Lotion 	Apply once daily
Adapalene/benzoyl peroxide (Epiduo; Epiduo Forte)	FDA-approved for acne	<ul style="list-style-type: none"> • Gel 	Apply once daily
Azelaic acid (Azelex)	FDA-approved for acne	<ul style="list-style-type: none"> • Cream 	Apply twice daily
Benzoyl peroxide (many brand names)	FDA-approved for acne	<ul style="list-style-type: none"> • Bar • Cream • Foam • Gel • Kits (miscellaneous formulations) • Liquid • Extended release liquid • Lotion • Foaming cloths 	<p>Topical formulations: apply once daily; gradually increase to 2-3 times/day if needed</p> <p>Topical cleansers: wash once or twice daily</p>
Clindamycin (Cleocin T; ClindaMax; Clindagel, Evoclin)	FDA-approved for acne	<ul style="list-style-type: none"> • Foam • Gel • Lotion • Solution 	<p>-Gel (Cleocin; ClindaMax), lotion, solution: apply twice daily</p> <p>-Gel (Clindagel), foam (Evoclin): apply once daily</p>
Dapsone (Aczone)	FDA-approved for acne	<ul style="list-style-type: none"> • Gel 	<p>-5%: apply twice daily</p> <p>-7.5%: apply once daily</p>
Erythromycin (Ery; Erygel)	FDA-approved for acne	<ul style="list-style-type: none"> • Gel 	-Gel: apply once or twice daily

		<ul style="list-style-type: none"> • Pad • Solution 	-Ointment, pads: apply twice daily
Sulfacetamide (Klaron)	FDA-approved for acne	<ul style="list-style-type: none"> • Lotion 	Apply twice daily
Tazarotene (Fabior; Tazorac)	FDA-approved for acne	<ul style="list-style-type: none"> • Cream • Foam • Gel 	Apply once daily
Tretinoin (Atralin; Avita; Refissa; Renova; Renova Pump; Retin-A; Retin-A Micr; Retin-A Micro Pump)	FDA-approved for acne	<ul style="list-style-type: none"> • Cream • Gel 	Apply once daily
ORAL SYSTEMIC ANTIBIOTICS			
Azithromycin (Zithromax; Zithromax Tri-Pak; Zithromax Z-Pak; Zmax)	Used off-label for acne	<ul style="list-style-type: none"> • Packet • Suspension reconstituted • Tablet 	As adjunct to topical acne therapy: regimens in clinical trials have varied greatly but all used pulse-dosing regimens. Use shortest duration possible to minimize development of bacterial resistance.
Doxycycline (Acticlate; avidoxy; Doryx; Doryx MPC; Monodoxyne NL; Morgidox; Okebo; Oracea; Soloxide; TargaDOX; Vibramycin)	Used off-label for acne	<ul style="list-style-type: none"> • Capsule as hyclate • Capsule as monohydrate • Capsule delayed release as monohydrate • Kit as hyclate • Suspension reconstituted as monohydrate • Syrup as calcium • Tablet as hyclate • Tablet as monohydrate • Tablet delayed release as hyclate 	<ul style="list-style-type: none"> -Immediate release: 50-100 mg twice daily or 100 mg once daily -Extended release: 100 mg twice daily on day 1, then 100 mg once daily
Erythromycin (E.E.S 400, E.E.S. Granules; Ery-Tab; EryPed 200; EryPed 400; Erythrocin Stearate)	Used off-label for acne	<ul style="list-style-type: none"> • Capsule delayed release particles as base • Suspension reconstituted as ethylsuccinate • Tablet as base • Tablet as ethylsuccinate • Tablet as stearate • Tablet delayed release as base 	250-500 mg (base) twice daily initially, followed by 250-500 mg (base) once daily
Minocycline (Minocin; Ximino)	FDA-approved for acne and inflammatory, non-nodular, moderate to severe acne	<ul style="list-style-type: none"> • Capsule • Capsule extended release • Tablet 	<p>Acne: 50-100mg twice daily</p> <p>Acne (inflammatory, non-nodular, moderate to severe):</p> <ul style="list-style-type: none"> -Extended-release capsule: 1 mg/kg once daily -Extended-release tablet: weight-based (various strengths)
Tetracycline	FDA-approved for acne	<ul style="list-style-type: none"> • Capsule 	Initial dose 1 g daily in divided doses; reduce gradually to 125-500 mg/day once improvement noted
Trimethoprim (Primsol; Trimplex)	Used off-label for acne	<ul style="list-style-type: none"> • Solution • Tablet 	100 mg 3 times daily or 300 mg twice daily
HORMONAL AGENTS			
Oral contraceptives	FDA-approved for acne	<ul style="list-style-type: none"> • Various 	Usual dosing: once daily

	(varies by formulation)		
Spirolactone (Aldactone, CaroSpir)	Used off-label for acne	<ul style="list-style-type: none"> • Suspension • Tablet 	Females: 50-200 mg once daily
ORAL ISOTRETINOIN			
Isotretinoin (Absorica; Amnesteem; Claravis; Myorisan; Zenatane)	FDA-approved for severe recalcitrant nodular acne	<ul style="list-style-type: none"> • Capsule 	0.5 to 1 mg/kg/day in 2 divided doses for 15-20 weeks; may discontinue earlier if total cyst count decreases by >70%; may require adjustment up to 2 mg/kg/day for adults with very severe disease/scarring or primarily involves the trunk

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane Collaboration – Minocycline

In 2012, the Cochrane Collaboration published an update to a 2000 systematic review assessing the efficacy and safety of minocycline in acne vulgaris.¹⁷ This review identified 39 RCTs.¹⁷ In general, it was found that minocycline is an effective treatment for moderate to moderately-severe acne vulgaris, but there is a lack of evidence to show superiority over other treatments.¹⁷ Of the 39 trials, 24 included patients with severe acne but only three trials included severe acne exclusively.¹⁷ Two of the three trials in severe acne compared minocycline to oral isotretinoin.¹⁷ Both of these trials were open-label and of poor quality.¹⁷ The third trial in severe acne was a fair quality double-blind 12 week RCT which compared minocycline 100 mg daily to doxycycline 100 mg daily.¹⁷ Both groups in the trial also received 5% salicylic acid/5% resorcinol topically twice a day.¹⁷ No difference was found between the two groups in change in overall symptom score from baseline, but the data is limited by the low number of participants (n=18).¹⁷

After review, 16 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), population studied (non-severe acne), or outcome studied (e.g., non-clinical).¹⁸⁻³³

Guidelines:

High Quality Guidelines:

None identified.

Additional Guidelines for Clinical Context:

American Academy of Dermatology: Acne Vulgaris

In 2016, the American Academy of Dermatology published an updated guideline for the management of acne vulgaris.⁵ Based on conflict of interest methodology, this guideline is not of high quality as one of the two co-chairs has served on an advisory board for four pharmaceutical companies, receiving honoraria and also served as a consultant for a fifth pharmaceutical company, receiving honoraria.⁵ Less than half of the work group (10/22 members) had no relevant relationships to disclose.⁵

Recommendations for treatment of severe acne are outlined in **Table 2.**⁵

Table 2. American Academy of Dermatology Severe Acne Treatment Recommendations⁵

1st line treatment	Oral Antibiotic (tetracyclines generally recommended first-line) + Topical combination therapy (fixed combination or separate products for one of the following): <ul style="list-style-type: none">• Benzoyl peroxide + antibiotic• Retinoid + benzoyl peroxide• Retinoid + benzoyl peroxide + antibiotic OR Oral isotretinoin
Alternative treatment	Consider change in oral antibiotic OR Add combined oral contraceptive or oral spironolactone (females) OR Consider oral isotretinoin

For mild and moderate acne, treatment options generally include all of the same agents recommended for severe acne alone or in different combinations.⁵ Oral isotretinoin is the only unique agent recommended as first-line therapy for severe acne but not recommended first-line for mild or moderate acne, though it may be considered as an alternative treatment for moderate acne.⁵ Recommendations for isotretinoin specifically include:

- Isotretinoin is a recommended treatment option for severe nodular acne.⁵
- Isotretinoin is appropriate for treatment of treatment-resistant moderate acne or management of acne producing physical scarring or psychosocial distress.⁵
- Low-dose isotretinoin can be effective in acne treatment and reduce frequency and severity of side effects.⁵ Intermittent dosing is not recommended.⁵
- Routine monitoring is recommended for liver function tests, serum cholesterol, and triglycerides at baseline and until response to treatment is established.⁵ Routine complete blood count monitoring is not recommended.⁵
- All patients must adhere to iPLEDGE™ risk management program.⁵
- Females of child-bearing potential should be counseled on contraceptive methods.⁵
- Patients should be educated on potential risks of therapy and monitored for indications of inflammatory bowel disease and depressive symptoms.⁵

Journal of the European Academy of Dermatology and Venerology: Acne

In 2012, the Journal of the European Academy of Dermatology and Venerology published the European Evidence-based Guidelines for the Treatment of Acne.⁴ Based on conflict of interest methodology, this guideline is not of high quality as no conflict of interest mitigation strategies are documented for the creation of the guideline.⁴ Additionally, the guideline was funded by the European Dermatology Forum (EDF), which has several pharmaceutical manufacturers listed as corporate partners, and the role of the funding source was not documented.^{4,34} The lead author on the guideline also disclosed several conflicts of interest including institution grants from EDF, the sponsor of the guideline, for efforts on the guideline.⁴

Recommendations for treatment of severe types of acne are outlined in **Table 3.**⁴

Table 3. Journal of the European Academy of Dermatology and Venerology Severe Acne Treatment Recommendations⁴

Strength of Recommendation	Severe Papulopustular/Moderate Nodular Acne	Severe Nodular/Conglobate Acne
High	Isotretinoin	Isotretinoin
Medium	Systemic antibiotics + adapalene, or Systemic antibiotics + azelaic acid, or Systemic antibiotics + adapalene + benzoyl peroxide	Systemic antibiotics + azelaic acid
Low	Systemic antibiotics + benzoyl peroxide	Systemic antibiotics + benzoyl peroxide, or Systemic antibiotics + adapalene, or Systemic antibiotics + adapalene + benzoyl peroxide
Alternatives for Female Patients	Hormonal antiandrogens + topical treatment, or Hormonal antiandrogens + systemic antibiotics	Hormonal antiandrogens + systemic antibiotics

The guideline also provides recommendations for non-severe forms of acne.⁴ Treatment recommended for comedonal acne includes topical retinoids (medium strength of recommendation), azelaic acid, or benzoyl peroxide (low strength of recommendation).⁴ Treatments for mild-to-moderate papulopustular acne with high strength of recommendation include adapalene in combination with benzoyl peroxide or benzoyl peroxide in combination with clindamycin.⁴ Multiple other treatments are also recommended based on medium and low strength of evidence.⁴

American Academy of Pediatrics: Pediatric Acne

In 2013, the American Acne and Rosacea Society (AARS) created a guideline on pediatric acne which was published and endorsed by the American Academy of Pediatrics (AAP).³ Based on conflict of interest methodology, this guideline is not of high quality as conflicts of interest for authors are not available.³ Therefore, it is not possible to evaluate the potential risk of bias.³ It is noted that no corporate benefactor of the AARS or AAP had any input into content preparation, data review, or any involvement in the outcome of the meeting or publication.³

Recommendations for treatment of severe types of acne are outlined in **Table 4.**³

Table 4. AARS/AAP Pediatric Severe Acne Treatment Recommendations³

Initial Treatment	Combination therapy: Oral antibiotic + topical retinoid + benzoyl peroxide +/- topical antibiotic
Inadequate Response	Consider changing oral antibiotic, and Consider oral isotretinoin Females: consider hormonal therapy

The guideline also provides recommendations for non-severe forms of acne. Recommendations for pediatric initial treatment of mild and moderate acne include the following:

- Mild acne³:
 - Benzoyl peroxide or topical retinoid, OR
 - Topical combination therapy:
 - Benzoyl peroxide + antibiotic, OR
 - Retinoid + benzoyl peroxide, OR
 - Retinoid + antibiotic + benzoyl peroxide
- Moderate acne³:
 - Topical combination therapy:
 - Retinoid + benzoyl peroxide, OR
 - Retinoid + benzoyl peroxide + antibiotic, OR
 - Retinoid + antibiotic + benzoyl peroxide, OR
 - Oral antibiotic + (topical retinoid + BP) or (topical retinoid + antibiotic + benzoyl peroxide)

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Appendix 1: Current Status of PDL Class

RouteDesc	FormDesc	Brand	Generic	PDL
TOPICAL	GEL (GRAM)	ADAPALENE	adapalene	
TOPICAL	GEL (GRAM)	DIFFERIN	adapalene	
TOPICAL	CREAM (G)	ADAPALENE	adapalene	
TOPICAL	CREAM (G)	DIFFERIN	adapalene	
TOPICAL	SOLUTION	ADAPALENE	adapalene	
TOPICAL	MED. SWAB	PLIXDA	adapalene	
TOPICAL	LOTION	DIFFERIN	adapalene	
TOPICAL	GEL W/PUMP	ADAPALENE	adapalene	
TOPICAL	GEL W/PUMP	DIFFERIN	adapalene	
TOPICAL	GEL W/PUMP	ADAPALENE-BENZOYL PEROXIDE	adapalene/benzoyl peroxide	
TOPICAL	GEL W/PUMP	EPIDUO	adapalene/benzoyl peroxide	
TOPICAL	GEL W/PUMP	EPIDUO FORTE	adapalene/benzoyl peroxide	
TOPICAL	FOAM	FINACEA	azelaic acid	
TOPICAL	CREAM (G)	AZELEX	azelaic acid	
TOPICAL	CREAM (G)	FINEVIN	azelaic acid	
TOPICAL	BAR	PANOXYL	benzoyl peroxide	
TOPICAL	GEL (GRAM)	ACNE MEDICATION	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZAC W 10	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZAC W 2.5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	PANOXYL AQ 2.5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZAC W 5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	DEL-AQUA-5	benzoyl peroxide	
TOPICAL	GEL (GRAM)	PANOXYL AQ 5	benzoyl peroxide	
TOPICAL	CREAM (G)	CLEARASIL DAILY CLEAR	benzoyl peroxide	
TOPICAL	CREAM (G)	DEL-AQUA-10	benzoyl peroxide	
TOPICAL	LOTION	ACNE MEDICATION	benzoyl peroxide	
TOPICAL	LOTION	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	CLEANSER	PANOXYL-4	benzoyl peroxide	
TOPICAL	CLEANSER	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	CLEANSER	PANOXYL	benzoyl peroxide	
TOPICAL	CLEANSER	PACNEX	benzoyl peroxide	
TOPICAL	FOAM	BENZOYL PEROXIDE	benzoyl peroxide	
TOPICAL	GEL (GRAM)	BENZACLIN	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	CLINDAMYCIN-BENZOYL PEROXIDE	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOS-BENZOYL PEROX	clindamycin phos/benzoyl perox	

TOPICAL	GEL (GRAM)	DUAC	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	NEUAC	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	BENZAACLIN	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	CLINDAMYCIN-BENZOYL PEROXIDE	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	ACANYA CLINDAMYCIN PHOS-BENZOYL	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	PEROX	clindamycin phos/benzoyl perox	
TOPICAL	GEL W/PUMP	ONEXTON	clindamycin phos/benzoyl perox	
TOPICAL	GEL (GRAM)	ONEXTON	clindamycin phos/benzoyl perox	
TOPICAL	KIT	CLINDACIN ETZ	clindamycin phos/skin clnsr 19	N
TOPICAL	KIT	CLINDACIN PAC	clindamycin phos/skin clnsr 19	N
TOPICAL	GEL (GRAM)	CLEOCIN T	clindamycin phosphate	N
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	SOLUTION	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	LOTION	CLEOCIN T	clindamycin phosphate	N
TOPICAL	LOTION	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLEOCIN T	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLINDACIN ETZ	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLINDACIN P	clindamycin phosphate	N
TOPICAL	MED. SWAB	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	FOAM	CLINDAMYCIN PHOSPHATE	clindamycin phosphate	N
TOPICAL	FOAM	EVOCLIN	clindamycin phosphate	N
TOPICAL	CMB CR GEL	NEUAC	clindamycin/benzoyl/emol cmb94	
TOPICAL	GEL (GRAM)	CLINDAMYCIN PHOS-TRETINOIN	clindamycin/tretinoin	
TOPICAL	GEL (GRAM)	ZIANA	clindamycin/tretinoin	
TOPICAL	GEL (GRAM)	ACZONE	dapsone	
TOPICAL	GEL (GRAM)	DAPSONE	dapsone	
TOPICAL	GEL W/PUMP	ACZONE	dapsone	
TOPICAL	SOLUTION	DEL-MYCIN	erythromycin base	N
TOPICAL	MED. SWAB	ERY	erythromycin base in ethanol	N
TOPICAL	MED. SWAB	ERYTHROMYCIN	erythromycin base in ethanol	N
TOPICAL	GEL (GRAM)	ERYGEL	erythromycin base in ethanol	N
TOPICAL	GEL (GRAM)	ERYTHROMYCIN	erythromycin base in ethanol	N
TOPICAL	SOLUTION	ERYTHROMYCIN	erythromycin base in ethanol	N
TOPICAL	GEL (GRAM)	BENZAMYCIN ERYTHROMYCIN-BENZOYL	erythromycin/benzoyl peroxide	N
TOPICAL	GEL (GRAM)	PEROXIDE	erythromycin/benzoyl peroxide	N
TOPICAL	GEL (EA)	BENZAMYCINPAK	erythromycin/benzoyl peroxide	N
ORAL	CAPSULE	ABSORICA	isotretinoin	
ORAL	CAPSULE	AMNESTEEM	isotretinoin	

ORAL	CAPSULE	CLARAVIS	isotretinoin
ORAL	CAPSULE	ISOTRETINOIN	isotretinoin
ORAL	CAPSULE	MYORISAN	isotretinoin
ORAL	CAPSULE	ZENATANE	isotretinoin
TOPICAL	SUSPENSION	KLARON	sulfacetamide sodium
TOPICAL	SUSPENSION	SULFACETAMIDE SODIUM	sulfacetamide sodium
TOPICAL	FOAM	FABIOR	tazarotene
TOPICAL	GEL (GRAM)	RETIN-A	tretinoin
TOPICAL	GEL (GRAM)	TRETINOIN	tretinoin
TOPICAL	GEL (GRAM)	AVITA	tretinoin
TOPICAL	CREAM (G)	AVITA	tretinoin
TOPICAL	CREAM (G)	RETIN-A	tretinoin
TOPICAL	CREAM (G)	TRETINOIN	tretinoin
TOPICAL	GEL (GRAM)	ATRALIN	tretinoin
TOPICAL	GEL (GRAM)	RETIN-A MICRO	tretinoin microspheres
TOPICAL	GEL (GRAM)	TRETINOIN MICROSPHERE	tretinoin microspheres
TOPICAL	GEL W/PUMP	RETIN-A MICRO PUMP	tretinoin microspheres
TOPICAL	GEL W/PUMP	TRETINOIN MICROSPHERE	tretinoin microspheres

Appendix 2: Specific Drug Information for Medications in the Acne Class

Table 5. Clinical Pharmacology and Pharmacokinetics (for medications in the Acne class; non-acne formulations excluded)^{6,16}

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
TOPICAL THERAPIES				
Adapalene	Retinoid-like compound	Minimal	Excretion: bile	• Half-life: 7-51 hours
Adapalene/benzoyl peroxide	Retinoid-like compound/ free-radical oxygen releaser	Via skin	<i>Metabolism</i> -Benzoyl peroxide: converted to benzoic acid in skin <i>Excretion</i> -Adapalene: primarily through bile -Benzoyl peroxide: urine	NA
Azelaic acid	Unknown; may decrease microcomedo formation	Cream: ~3-5% penetrates stratum corneum; up to 10% found in epidermis and dermis; 4% systemic	Metabolism: negligible after topical application; some beta-oxidation to shorter chain dicarboxylic acids Excretion: urine (primarily as unchanged drug)	• Half-life: 12 hours
Benzoyl peroxide	Releases free-radical oxygen	~5% via skin; gel more penetrating than cream	Metabolism: converted to benzoic acid in skin	NA
Clindamycin	Lincosamide antibiotic	Minimal for topical solution or foam	Metabolism: hepatic; forms metabolites (variable activity); clindamycin phosphate is converted to clindamycin HCl Excretion: urine (<0.2% with topical foam and solution)	NA
Dapsone	Unknown; may act as enzyme inhibitor or oxidizing agent; has numerous immunologic effects	~1% of the absorption of 100 mg tablet	NA	NA
Erythromycin	Macrolide antibiotic	NA	NA	NA
Salicylic acid	Produces desquamation of hyperkeratotic epithelium	Gel: >60% (under occlusion)	Excretion: urine	NA
Sulfacetamide	Sulfonamide derivative antibiotic	Significant absorption through skin; percutaneous absorption ~4%	Metabolism: sulfanilamide (major metabolite) Excretion: urine 0.08%-0.33%	• Half-life: 7-13 hours
Tazarotene	Synthetic, acetylenic retinoid	Minimal following cutaneous applications (≤6% of dose)	Metabolism: prodrug, rapidly metabolized via esterase hydrolysis to an active metabolite (tazarotenic acid) following topical application and systemic absorption; tazarotenic acid undergoes further hepatic metabolism Excretion: urine and feces (as metabolites)	• Half-life: ~18 hours (cream, gel) or 8.1 hours (foam)
Tretinoin	Vitamin A derivative	Minimal	Metabolism: hepatic; forms metabolites Excretion: urine and feces	NA
ISOTRETINOIN				
Isotretinoin	Reduces sebaceous gland size and reduces sebum production in acne treatment	Enhanced with high-fat meal; Absorica absorption is ~83% greater than Accutane when	Metabolism: hepatic via CYP2B6, 2C8, 2C9, 3A4; forms metabolites; major metabolite: 4-oxo-isotretinoin (active)	• Half-life: 21 hours (parent drug); 21-24 hours (metabolite)

		administered under fasting conditions; they are bioequivalent when taken with a high-fat meal	Excretion: urine and feces (equal amounts)	
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Abbreviations: NA = not applicable

Table 6. Use in Specific Populations (for medications in the Acne class)^{6,16}:

Drug Name	Warnings for Use in Pediatrics	Warnings for Use in Renal Impairment	Warnings for Use in Hepatic Impairment	Warnings for Use in Pregnancy
TOPICAL AGENTS				
Adapalene	NA	NA	NA	Adverse effects were observed in animal reproduction studies. Retinoids may cause harm when administered during pregnancy.
Adapalene/benzoyl peroxide	NA	NA	NA	Animal reproduction studies have not been conducted with this combination. Refer to individual drugs.
Azelaic acid	NA	NA	NA	Adverse events have been observed in animal reproduction studies following oral administration. The amount of azelaic acid available systemically following topical administration is minimal (<4%).
Benzoyl peroxide	NA	NA	NA	Topical products are recommended as initial therapy for the treatment of acne in pregnant females; benzoyl peroxide is one of the preferred agents.
Clindamycin	NA	NA	NA	If treatment for acne is needed during pregnancy, topical clindamycin may be considered if an antibiotic is needed. To decrease systemic exposure, pregnant women should avoid application to inflamed skin for long periods of time, or to large body surface areas.
Dapsone	NA	NA	NA	Topical products are recommended as initial therapy for the treatment of acne vulgaris in pregnant females; however, information specific to dapsone is lacking. Agents other than topical dapsone are preferred.
Erythromycin	NA	NA	NA	The amount of erythromycin available systemically following topical application is considered to be very low. Systemic absorption would be required in order for erythromycin to cross the placenta and reach the fetus. Topical erythromycin may be used for the treatment of acne in pregnancy.
Salicylic acid	Avoid prolonged use over large areas; may result in salicylism. Limit application area in children <12 years of age. Use may be associated with Reye syndrome; use caution in children or adolescents with varicella or influenza. Some products are contraindicated in children <2 years	Avoid prolonged use over large areas in patients with significant renal impairment; may result in salicylism	Avoid prolonged use over large areas in patients with significant hepatic impairment; may result in salicylism	For the topical treatment of acne or warts, salicylic acid can be used in pregnant women if the area of exposure and duration of therapy is limited, although other agents may be preferred

Sulfacetamide	NA	NA	NA	Amount systemically available after topical administration is unknown. Use of systemic sulfonamides during pregnancy may cause kernicterus in the newborn.
Tazarotene	NA	NA	NA	Use in pregnancy is contraindicated.
Tretinoin	NA	NA	NA	Adverse events were observed in animal reproduction studies following topical application of tretinoin. Teratogenic effects were also observed in pregnant women following topical use; however, a causal association has not been established. When treatment for acne is needed during pregnancy, other agents are preferred
ISOTRETINOIN				
Isotretinoin	NA	NA	Clinical hepatitis and mild to moderate elevated liver enzymes have been reported with use; liver enzymes may normalize with dosage reduction or with continued treatment. Discontinue therapy if hepatic enzymes do not normalize or if hepatitis is suspected	Use is contraindicated in females who are or may become pregnant; REMS program (iPLEDGE™) required.

Abbreviations: NA = not applicable

Drug Safety for Medications in the Acne Class:

Boxed Warnings^{6,16}:

- *Isotretinoin*: Must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin. Because of the teratogenicity, it is approved for marketing only under a special restricted distribution called iPLEDGE™.
- *Tretinoin*: Patients with acute promyelocytic leukemia (APL) can have severe adverse reactions to tretinoin including retinoic acid-APL (RA-APL) syndrome characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, edema, and hepatic, renal, and multi-organ failure.

Risk Evaluation Mitigation Strategy Programs^{6,16}:

- *Isotretinoin*: Goal of the program is to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions.

Contraindications^{6,16}:

- *Adapalene*: hypersensitivity to adapalene or any of the components of the product
- *Benzoyl peroxide*: hypersensitivity to benzoyl peroxide or to any component of the product

- *Clindamycin*: history of antibiotic-associated colitis, including pseudomembranous colitis; history of regional enteritis; history of ulcerative colitis; hypersensitivity to clindamycin or other lincosamides, such as lincomycin
- *Erythromycin*: hypersensitivity to erythromycin or any component of the product
- *Isotretinoin*: hypersensitivity to isotretinoin or any of its components; hypersensitivity to vitamin A; pregnancy, known or suspected (risk of teratogenic effects; required to use 2 effective contraception methods or continuous abstinence for 1 month prior, during, and 1 month after isotretinoin therapy)
- *Sulfacetamide*: hypersensitivity to sulfonamides or any component of the formulation; kidney disease (Ovace Plus Wash, Ovace Plus Lotion, Ovace Plus foam)
- *Tazarotene*: hypersensitivity to tazarotene or any component of the product; pregnancy
- *Tretinoin*: hypersensitivity to tretinoin or any component of the product; sensitivity to parabens (preservative in oral gelatin capsules)

Table 7. Summary of Warnings and Precautions for Medications in the Acne Class^{6,16}

Warning/ Precaution	TOPICAL AGENTS										
	Adapalene	Adapalene/ benzoyl peroxide	Tretinoin	Tazarotene	Benzoyl peroxide	Salicylic acid	Dapsone	Azelaic acid	Clindamycin	Erythromycin	Sulfacetamide
Hypersensitivity reactions	X		X		X	X		X			X
Photosensitivity	X	X	X	X							
Skin irritation	X	X	X	X	X			X			
Avoid use with sulfone products		X			X						
Bleaching effects		X			X						
Drug-drug interactions		X	X				X				X
Fish allergies			X (Atralin)								
Caution in eczema			X								
Avoid use with salicylates						X					
Localized discoloration							X				
Hemolysis							X				
Methemoglobinemia							X				
Hypopigmentation								X			
Asthma exacerbation								X			
Colitis									X		
Caution in atopic patients									X		
Superinfection										X	
Cumulative irritation with concurrent topical acne therapy										X	
Autoimmune effects, blood dyscrasias, dermatologic reactions, hepatic effects: fatalities associated with severe reactions											X

Sulfonamide ("sulfa") allergy											X
Systemic effects with application to large, infected, abraded, denuded, or burned skin											X
Infection with nonsusceptible organisms											X
Metabisulfites-allergy											X
Not compatible with silver-containing products											X

Summary of Warnings and Precautions for Isotretinoin^{6,16}

- Concerns related to adverse effects
 - Auditory impairment
 - Bone mineral density loss
 - Dermatologic effects
 - Growth effects
 - Hematologic effects
 - Hepatic effects
 - Hypersensitivity reactions
 - Inflammatory bowel disease
 - Musculoskeletal effects
 - Ocular effects
 - Pancreatitis
 - Photosensitivity
 - Pseudotumor cerebri
 - Psychiatric effects
- Disease-related concerns
 - Use with caution in patients with diabetes
 - Use with caution in patients with hypertriglyceridemia or those who may be at high risk
- Concurrent drug therapy issues
 - Potential significant drug-drug interactions may exist
- Other warnings/precautions
 - Patients should not donate blood during therapy and for 1 month following discontinuation of therapy due to risk of donated blood being given to a pregnant female
 - Should only be prescribed by health care providers competent in treating severe recalcitrant nodular acne and experienced with the use of systemic retinoids
 - Safety of long-term use is not established and not recommended; effect on bone loss is unknown
 - Avoid skin resurfacing procedures
 - REMS program (iPLEDGE™) required for all patients, prescribers, wholesalers, and dispensing pharmacists

Appendix 3: Medline Search Strategy on 08/28/2018

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to August 03, 2018

1 exp TRETINOIN	21313
2 exp ADAPALENE, BENZOYL PEROXIDE DRUG COMBINATION/ or exp ADAPALENE/	337
3 tazarotene.mp.	475
4 exp ISOTRETINOIN/	3350
5 exp Benzoyl Peroxide/	1054
6 exp CLINDAMYCIN/	5436
7 exp ERYTHROMYCIN/	23830
8 exp DAPSONE/	4665
9 azelaic acid.mp.	578
10 exp Salicylic Acid/	7869
11 exp TETRACYCLINE/	19335
12 exp DOXYCYCLINE/	8941
13 exp MINOCYCLINE/	5533
14 exp TRIMETHOPRIM/	11473
15 exp AZITHROMYCIN/	4584
16 exp Contraceptives, Oral/	44530
17 exp SPIRONOLACTONE/	6450
18 exp SULFACETAMIDE/	348
19 exp SULFUR/	23859
20 acne.mp. or exp Acne Vulgaris/	15114
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	180130
22 20 and 21	4603
23 limit 22 to (English language and humans)	3705
24 limit 23 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	1153
25 limit 24 to yr="2003-Current"	602

Appendix 4: Key Inclusion Criteria

Population	Patients with severe cystic acne, acne conglobata, or acne fulminans
Intervention	<ul style="list-style-type: none">• Topical agents: adapalene, adapalene/benzoyl peroxide, tretinoin, tazarotene, benzoyl peroxide, salicylic acid, dapsone, azelaic acid, clindamycin, erythromycin, sulfacetamide• Oral systemic antibiotics: doxycycline, minocycline, tetracycline, azithromycin, erythromycin, clindamycin, trimethoprim, and sulfamethoxazole/trimethoprim• Hormonal agents: oral contraceptives and spironolactone• Oral isotretinoin
Comparator	Any drug in the “Intervention” inclusion criteria
Outcomes	Symptom improvement; quality of life; severe adverse events
Timing	Any study length; lit search from 1/1/2003-08/06/2018
Setting	Outpatient

Acne Medications

Goal(s):

- Ensure that medications for acne are used appropriately for OHP-funded conditions.

Length of Authorization:

Up to 12 months

Requires PA:

- All drugs in the Acne medications class

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	Yes: Go to #4	No: Pass to RPh. Deny; not funded by the OHP.
4. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. 	Yes: Inform prescriber of covered alternatives in class.	No: Approve for 12 months.

