Azelaic Acid (FINACEA) Topical Foam 15%

National Drug Monograph
August 2016
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Azelaic acid is a naturally occurring C9-dicarboxylic acid that is found in plants (such as whole grain cereals), animals and humans. Azelaic acid has antiinflammatory, antioxidative and antikeratinizing effects. In rosacea skin, azelaic acid decreases cathelicidin levels and kallikrein 5 (KLK5) activity and possibly inhibits toll-like receptor 2 (TLR2) expression.[1] A 15% gel formulation has been marketed for rosacea, and 20% cream has been available for acne vulgaris. The newer foam formulation consists of an oil-in-water emulsion and was designed to have a higher lipid content than the gel for dry and sensitive skin.
Indication(s) Under Review in This Document	Topical treatment of inflammatory papules and pustules of mild to moderate rosacea.
Dosage Form(s) Under Review	Foam, 15%
REMS	☐ **REMS** ☒ **No REMS** ☐ **Postmarketing Requirements** See Other Considerations for additional REMS information
Pregnancy Rating	Category B

Executive Summary	
Efficacy	• There have been no head-to-head trials comparing the foam and gel formulations of azelaic acid in terms of safety, tolerability and efficacy in the treatment of papulopustular (PP) rosacea.. • In two major randomized clinical trials, azelaic acid foam produced small benefits over vehicle foam in achieving Investigator's Global Assessment (IGA) treatment success (NNTs of 9.2 and 11.5) and in reducing inflammatory lesion counts. • Azelaic acid foam reduced inflammatory erythema but was ineffective in improving telangiectasias.
Safety	• Contraindications: None • Warnings / Precautions: Hypopigmentation, eye irritation, flammable propellant. • Common Adverse Reactions: Application site pain, pruritus, dryness, erythema. • Application site adverse events were generally mild to moderate, occurred early in treatment and were transient, with most events in the azelaic acid foam group lasting no longer than 1 hour.
Other Considerations	• The two major efficacy-safety trials included patients with *moderate to severe* PP rosacea (with the majority [86.8%–90.0%] having moderate disease); however, the FDA approved azelaic acid foam for treatment of *mild to moderate* PP rosacea. • The foam and gel formulations of azelaic acid have not been compared in a clinical study. • A generic azelaic acid gel (15%) product is tentatively approved and is not yet marketed.

	• Storage and Handling. WARNING: Flammable. Need to avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Must not puncture or incinerate. Must not expose to heat or store at temperatures above 120°F (49°C).
Projected Place in Therapy	• Azelaic acid topical foam would provide benefit for reducing inflammatory lesions in patients with mainly moderate PP rosacea and may be used as an alternative to azelaic acid gel 15%, with consideration given to relative product costs and patient preference. • Azelaic acid is considered to be first-line therapy and may be useful in combination with either other topical agents or oral agents.

Background

Purpose for Review

FDA approval of new formulation with supportive randomized clinical trials (RCTs)

Issues to be determined:
- ✔ Does azelaic acid foam offer efficacy advantages over available alternatives?
- ✔ Does azelaic acid foam offer safety advantages over available alternatives?
- ✔ Are there subgroup response predictors for safety or efficacy of this product?

Other Therapeutic Options

Alternative topical treatments at approximately the same step in therapy for mild to moderate papulopustular (PP) rosacea are listed in the table below (source, UpToDate[2]).

Formulary Alternatives	Dose and Effects	Other Considerations
FDA-approved for Mild–Moderate PP Rosacea		
Benzoyl Peroxide Topical Gel 5%, 10%; Lotion 5%, 10%	Dose: Initially once daily; gradually increase to two to three times daily if needed.	Limited efficacy data. Bleaches towels and clothing.
Metronidazole Topical Cream or Gel 0.75%, 1%	Dose: Twice daily for 0.75% products. Once daily for 1% products. Onset: 2–4 wks Max Effects: 8–9 wks	Approved for treatment of inflammatory lesions and erythema of rosacea. Ineffective for facial telangiectasias. Relapse is common following discontinuation. Pregnancy category B.
Sulfacetamide Sodium-Sulfur Topical Lotion 10% / 5%	Dose: One to three times daily.	Approved as an aid in the treatment of "acne rosacea." Mechanism unknown. Limited efficacy data. May cause allergic reactions; avoid in patients with sulfa allergies. Has an unpleasant odor.
Used Off-label for PP Rosacea		
Benzoyl Peroxide / Clindamycin Topical Gel 5% / 1%	Clinical Study Dose: Once daily for 12 wks.	Bleaches towels and clothing. Combination may be more effective than clindamycin alone.
Clindamycin Phosphate Topical Lotion, Topical Solution / Topical Swab (all 1%)	Clinical Study Dose: Once or twice daily for 12 wks.	Efficacy data are limited and pertain to a lotion product. Concerns about antibiotic resistance.
Erythromycin Topical Gel	Dose: Twice daily.	Limited data suggest

2%, Solution 2%		benefit. Concerns about antibiotic resistance.
Permethrin Topical Cream 5% (Rx)	Clinical Study Doses: Once daily for 7 wks or twice daily for 8–15 wks.	Limited efficacy data. Mechanism may be related to anti-ectoparasitic effects against *Demodex folliculorum* mite. Long-term safety is unknown.
Tretinoin Cream 0.025%	Dose: Once daily at night.	Has antiinflammatory effects and repairs extracellular matrix. Variable efficacy results. May worsen underlying vascular disease and produce skin irritation. Retinoids and High-dose Vitamin A (Highly Teratogenic), Criteria for Use limit indication to acne vulgaris.

Nonformulary Alternatives	**Dose and Effects**	**Other Considerations**
FDA-approved for Mild–Moderate PP Rosacea		
Azelaic Acid (FINACEA, by Bayer HealthCare) Topical Gel 15%	Dose: Twice daily; however, once daily may be as effective as twice daily.[3] Onset: 2–4 wks Max effects: 12–15 wks	For treatment of the inflammatory papules and pustules of rosacea. May cause some reduction of erythema[4]; however, has not been evaluated for rosacea erythema in the absence of papules and pustules. Ineffective for facial telangiectasias. A generic gel product by Glenmark Pharms is tentatively approved and not yet marketed. Shown to be superior to metronidazole 0.75% gel[5] and similar to metronidazole 1% gel in reducing inflammatory lesion counts and erythema.[6]
Ivermectin Topical Cream 1%	Dose: Once daily	Approved for treatment of inflammatory lesions of rosacea in adult patients. Antiinflammatory and possibly antiparasitic (anti-*Demodex*) effects. Superior to metronidazole 0.75% cream in reducing inflammatory lesions[7] and maintaining remission[8] in moderate to severe PP rosacea. Criteria for Use.
Metronidazole Lotion 0.75%	Dose: Twice daily. Onset and Max Effects: See above.	See metronidazole above.

Sulfacetamide Sodium-Sulfur Topical Suspension, Cleanser, Cream, E-Green Emollient Cream, Emulsion, Foam, Liquid, Suspension, Cleansing Pads in various concentrations, most commonly 10% / 5%; low sulfur (LS) products contain 2% sulfur.	Dose: One to three times daily for all products except one to two times daily for cleansing products.	See sulfacetamide-sulfur lotion above. E-green emollient cream contains a color corrector. Low sulfur content reduces odor.
Used Off-label for PP Rosacea		
Adapalene Gel 0.1%	Dose: Once daily for up to 12 wks.	See tretinoin above. Adapalene is generally better tolerated than other retinoids.
Azelaic Acid (AZELEX, by Allergan) Topical Cream 20%	Dose: Twice daily Onset: 2–4 wks Max effects: 12–15 wks	FDA-approved for treatment of mild to moderate inflammatory acne vulgaris. Shown to be effective in reducing inflammatory lesions and erythema of PP rosacea,[9] and similar or superior to metronidazole 0.75% cream in reducing inflammatory lesions,[10,11] erythema[10,11] and skin dryness.[10]
Clindamycin Topical Gel 1%		See clindamycin above.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to 9 Jun 2016) and the Cochrane Central Register of Controlled Trials (issue 5 of 12, May 2016) using the search terms *azelaic acid* and *foam*. The search was limited to studies performed in humans. Reference lists of review articles were searched for relevant clinical trials. Clinical trial data were also obtained from the manufacturer's AMCP dossier[12] and the FDA Medical Review(s).[13] All relevant RCTs, comparative observational studies and long-term (≥ 1 year) studies were included.

Review of Efficacy

- The literature search found no studies that directly compared azelaic acid foam 15% with either other azelaic acid formulations (e.g., 15% gel, 20% cream) or other rosacea treatments.
- The FDA approval of azelaic acid foam was based mainly on two (one phase II and one phase III) double-blind placebo-controlled trials (Table 1).

Table 1 Overview of Clinical Trials

Trial	Purpose / Interventions	Population	Design (Status)
1401841 (15853)	Determine the irritation potential of azelaic acid foam using the 21-day cumulative irritancy test	40 healthy volunteers	Phase I DB VC IIC RCT
1401842 (15854)	Evaluate the sensitization potential of azelaic acid foam using an HRIPT	240 healthy volunteers	Phase I DB VC IIC RCT
1401843 (15386)	Determine the additional systemic exposure regarding the endogenously occurring substances azelaic acid and its metabolite pimelic acid, resulting from the treatment of	24 patients	Phase I CO SB RCT

Trial	Purpose / Interventions	Population	Design (Status)
	patients with azelaic acid foam versus azelaic acid gel		
1402140 (17171)	Compare the action of azelaic acid foam with its vehicle	83 patients with rosacea	Phase II MC (20 US sites) DB VC RCT
1403120 (14955)[14]	Major efficacy-safety trial Compare the efficacy and safety of azelaic acid foam with its vehicle in patients with rosacea AzAF vs. VF 0.5 g twice daily No other concomitant rosacea therapies were allowed. Average amount of AzAF used: 1.3 g/d	401 outpatients ≥ 18 years of age, PP rosacea (IGA score of moderate or severe), 12–50 inflammatory lesions (papules and/or pustules) and persistent erythema with or without telangiectasia. Excluded known nonresponders to AzA. Mean age 48.5 y; 91.5% < 65 y; 25.7% male; 96.5% white; 27.7% Hispanic / Latino. 90.0% had moderate rosacea using IGA score.	12-wk Phase II MC DB VC RCT (20 US sites) (Published)
1401846 (16080)[15]	Major efficacy-safety trial Compare the efficacy and safety of azelaic acid foam with its vehicle in patients with rosacea AzAF vs. VF twice daily No other concomitant rosacea therapies were allowed.	961 outpatients ≥ 18 years of age, PP rosacea (IGA score of moderate or severe), 12–50 inflammatory lesions (papules and/or pustules) and persistent erythema with or without telangiectasia. Excluded known nonresponders to AzA. Mean age 51.5 y; 82.8% < 65 y; 27.0% male; 95.5% white; 86.8% had moderate rosacea using IGA score.	12-wk Phase III MC DB VC RCT (48 US sites) (Published)

AzA(F), Azelaic acid (foam); CO, Crossover; DB, Double-blind; HRIPT, human repeat insult patch test IIC, Intraindividual comparison; MC, Multicenter; RCT, Randomized clinical trial; SB, Single (investigator)-blinded; VC, Vehicle-controlled; VF, Vehicle foam

Phase II Major Efficacy-Safety Trial 1403120

- Co-primary efficacy measures: Treatment success based on the Investigator's Global Assessment (IGA) scores and percent changes from baseline in inflammatory lesion count. Treatment success was defined as achieving a clear or minimal IGA with 2-step improvement.
- Secondary efficacy measures
  - IGA Response Rate – Clear, minimal or mild rating on IGA.
  - Percent Change in Inflammatory Lesion Count from baseline to end of therapy
- The results showed that azelaic acid foam produced a small benefit over vehicle foam in achieving IGA treatment success (NNT of 9.2) and in reducing inflammatory lesion count (Table 2).

Table 2 Week-12 Efficacy Results of the Phase II Major Efficacy-Safety Trial

Efficacy Measure	AzA Foam N = 198	Vehicle Foam N = 203	Diff	Comments
IGA Treatment Success, % of pts (Co-PEM)	43.4	32.5	10.9*	NNT = 9.2
Inflammatory Lesion Count, change from BL, mean (SD) (Co-PEM)	–13.4 (10.39)	–9.5 (9.73)	–3.9*	*g* = 0.39
IGA Response Rate, %	69.2	57.6	11.6*	NNT = 8.6
Percent Change in Inflammatory Lesion Count from BL	–64.1	–50.8	–13.3*	

* P ≤ 0.017. BL, Baseline; *g,* Hedge's *g*; PEM, Primary efficacy measure.

- Other efficacy measures
  - Onset of significant difference in IGA scores: Week 4 in the phase II pivotal trial.
  - Erythema Intensity: Inconsistent results within the phase II trial (azelaic acid foam was superior to vehicle in terms of mean scores at end of treatment (p = 0.003) but there was no significant difference in terms of the mean change in erythema intensity scores from baseline.
  - Facial skin color score: No significant treatment difference in the phase II pivotal trial.
  - Quality of Life (QoL): No significant treatment difference in the phase II pivotal trial.
  - Subject's Global Assessment (SGA) of Response, "Excellent" or "Good": Azelaic acid foam was superior to vehicle (117/198 [62.2%] vs. 86/203 [45.5%]) in the phase II pivotal trial.

- Subject's Opinion of Cosmetic Acceptability was "Very Good" or "Good": 66.5% vs. 60.8%
- Subject's Opinion of Local Tolerability was "Excellent" or "Good": Azelaic acid foam similar to vehicle (70.2% vs. 78.3%)

- Subgroup analyses showed no significant treatment differences in efficacy based on inflammatory lesion count at baseline, gender and age.

Phase III Major Efficacy-Safety Trial 1401846

- Co-primary Efficacy Measures: Same as for the phase II major efficacy-safety trial.
- Secondary Efficacy Measures
  - Percent change in inflammatory lesion count from baseline
  - IGA response rate (responder = clear, minimal or mild)
  - Grouped change in erythema rating – improved, no change or worsened
- The results were consistent with the phase II findings, showing that azelaic acid foam produced a small benefit over vehicle foam in achieving IGA treatment success (NNT of 11.5) and in reducing inflammatory lesion counts (Table 3). Active treatment had a small, significant benefit over vehicle foam in improving the intensity of erythema. The vehicle foam control group experienced substantial improvements from baseline, probably reflecting the beneficial effects of skin care achievable with the foam formulation.

Table 3 Week 12 Efficacy Results of the Phase III Major Efficacy-Safety Trial

Efficacy Measure	AzA Foam N = 483	Vehicle Foam N = 478	Diff	Comments
IGA Treatment Success, % of pts (Co-PEM)	32.1	23.4	8.7*	NNT = 11.5
Inflammatory Lesion Count, change from BL, mean (SD) (Co-PEM)	–13.2 (9.5)	–10.3 (9.8)	–2.9*	*g* = 0.29
IGA Response Rate, %	66.3	54.4	11.9*	NNT = 8.4
Percentage Change in Inflammatory Lesion Count from BL	–61.6	–50.8	–10.8*	
Change in Erythema Intensity from BL, % improvement	61.5	51.3	10.2*	

* P < 0.001. BL, Baseline; *g,* Hedge's *g*; PEM, Primary efficacy measure.

- Other Efficacy Measures (Azelaic Acid vs. Vehicle)
  - Erythema rating of "Clear" or "Almost Clear": 9.3% vs. 8.4%
  - Telangiectasia rating of "improvement": no significant treatment differences
  - Facial skin color: no significant treatment differences
  - Subject's global assessment of treatment response of "excellent" or "good": azelaic acid foam was superior (57.2% vs. 44.7%; difference, 12.5%; p < 0.001; NNT = 8)
  - Subject's global assessment of tolerability of "excellent" or "good": 67.8% vs. 78.2%
  - Subject's opinion on cosmetic acceptability of "very good" or "good": 66.2% vs. 61.6%
  - Subject's opinion on practicability of product use in facial areas next to the hairline of "very good" or "good": > 70% in both treatment groups
  - RosaQoL and EuroQoL Group Questionnaire-5 Dimensions (EQ-5D-5L), overall / summary score changes from baseline: no significant treatment differences
  - Dermatology Life Quality Index (DLQI) overall score, change from baseline: azelaic acid foam was superior (–2.6 vs. –2.1; p = 0.019)
- Subgroup analyses were not reported.

Cochrane Systematic Review / Meta-analysis Evaluating the Efficacy and Safety of Rosacea Treatments[16,17]

- This systematic review / meta-analysis was an update to a 2011 Cochrane review of rosacea treatments.[18]
- One of the 106 RCTs (N = 13,631; 9 RCTs in quantitative meta-analysis) evaluated azelaic acid topical foam 15% (the phase II trial by Draelos, et al., 2013; moderate quality evidence for lesion count[14]).
- The included studies evaluated treatments for any type of rosacea, with most studies involving patients with PP rosacea. Most studies did not specify the severity of rosacea.
- The evidence from placebo-controlled trials supported the effectiveness of the following agents:
  - Topical metronidazole – risk ratio (RR) 1.98 (95% CI 1.29 to 3.02) for physician assessments (K = 3; moderate quality). One study provided moderate quality evidence for remission rates: 9 (20.4%) of 44 patients relapsed on metronidazole versus 18 (40.9%) of 44 relapsed on placebo, for a RR of 0.50 (0.25 to 0.99). High-quality evidence from 6 studies (N = 1773) showed a higher incidence of adverse events

on metronidazole (191 per 1000; 95% CI 151 to 243) versus placebo (161 per 1000), with a RR of 1.19 (0.94 to 1.51). The RRs for other outcomes were not estimable.
    - Topical azelaic acid – RR 1.46 (95% CI 1.30 to 1.63) for participants' assessments (K = 4; high quality). See Table 4.
    - Topical ivermectin – RR 1.78 (1.50 to 2.11) and RR 1.92 (1.59 to 2.32) for participants' assessments in two studies (for moderate to severe PP rosacea; high quality) and oral subantimicrobial-dose (40 mg) doxycycline (high quality, based on physicians' assessments) for the treatment of PP rosacea.

Table 4 Azelaic Acid Versus Placebo in Rosacea

Outcome Measure	Risk with AzA per 1000 (95% CI)	Risk with PBO per 1000 (95% CI)	Relative Risk (95% CI)	N (K)	Comments
HRQoL	—	—	—	—	
PGA, marked improvement to complete remission	615 (548–687)	421	1.46 (1.3–1.63)	1179 (4)	
IGA of improvement	655 (586–730)	497	1.32 (1.18–1.47)	1179 (4)	
Erythema or Telangiectasia	—	—	NE	1245 (5)	Decrease in erythema ranged from 44%–47.9% for AzA and 28%–37.9% for PBO. Minimal changes in telangiectasia.
Lesion Count	3.90 lower (5.87–1.93 lower)	–9.5	—	401 (1)	Risk shown for AzA is relative to the risk with PBO. Reference 14 (phase II trial evaluating AzA foam 15% by Draelos, et al., 2013).
Time to Improvement of Lesions	—	—	NE	1245 (5)	Not a prespecified outcome. All studies showed clear improvement after 3–6 wks.
Duration of Remission	—	—	NE	—	
Proportion of Participants with Adverse Event	—	—	NE	1245 (5)	High quality evidence. RRs in 2 studies: • 1.00 (95% CI 0.62 to 1.62) • 2.39 (1.12 to 5.09), p = 0.02 Incidences in 3 studies (AzA vs. PBO): • 24/33 (72.7%) vs. 19/33 (57.6%) • 18% and 8% vs. No data

AzA, Topical azelaic acid; IGA, Investigator / Physician global assessment; NE, Not estimable; PBO, Placebo; PGA, Patient / Participant's global assessment

- There were a small number of trials comparing different active agents.
    - Three RCTs comparing topical metronidazole and topical azelaic acid showed inconsistent results about which agent was superior, and the evidence was low in quality.
    - Topical metronidazole and oral tetracycline were not statistically different in any of the outcome measures of interest (low–moderate quality evidence).
    - Topical ivermectin was slightly more effective than topical metronidazole in improving quality of life, participant and physician assessments and lesion counts (1 RCT; mainly high quality evidence).
    - Subantimicrobial doxycycline was shown to be as effective as 100-mg doxycycline and safer in adverse events (RR 0.25; 95% CI 0.11 to 0.54); however, the quality of evidence was low.
- Further studies evaluating treatments for ocular and phymatous rosacea are needed.

Potential Off-Label Use

- Acne
- Hyperpigmentation

Safety

For more detailed information, refer to the prescribing information.[19]

Boxed Warning	• None
Contraindications	• None
Warnings / Precautions	• Hypopigmentation (monitor) • Eye irritation (avoid contact with eyes; if contact with eyes occurs, rinse liberally with water and seek medical attention if irritation persists) • Propellant is flammable (avoid fire, flame, and smoking; do not puncture or incinerate; do not expose to heat or store at temperatures above 120°F (49°C).

Adverse Reactions

Common Adverse Reactions	• Application site pain (6.2%), pruritus (2.5%), dryness (0.7%), erythema (0.7%) • Cutaneous adverse events were more common on azelaic acid foam than vehicle (11.4% vs. 7.3%) and more likely to occur during the first 4 weeks of therapy. • Application site adverse events were generally mild to moderate, occurred early in treatment and were transient, with most events in the azelaic acid foam group lasting no longer than 1 hour.
Deaths / Serious Adverse Reactions	• Pooled data from all phase II and phase III RCTs: 1 death (head trauma, deemed unrelated to study drug) and 4 patients with SAEs on azelaic acid foam (3 in the phase III RCT [bilateral deep vein thrombosis, congestive heart failure and hepatotoxicity]) versus 7 patients with SAEs on vehicle. None of the SAEs were deemed to be related to study drug.
Discontinuations Due to Adverse Reactions	• Drug-related adverse events that led to discontinuation of azelaic acid foam included the following application site reactions: pain, erythema, dryness, papules, urticaria, dermatitis, erosion, hypersensitivity, and scab. In addition, drug-related adverse events that led to discontinuation included headache, urticaria and rosacea. • Phase II pivotal trial, azelaic acid foam vs. vehicle: 2.0% vs. 1.5% • Phase III pivotal trial: 1.2% vs. 2.5%

Other Safety Considerations

Postmarketing Experience	• Hypersensitivity, rash, worsening of asthma
Local Tolerability Studies	• In a 21-day cumulative irritation study under occlusive conditions, mild to moderate irritation was observed for azelaic acid pre-foam emulsion.[19] • In a human repeat insult patch test (**HRIPT**) study, no sensitization potential was observed for azelaic acid pre-foam emulsion.[19]

Drug Interactions

Drug-Drug Interactions	• No data in prescribing information.

Risk Evaluation

As of 8 June 2016

Sentinel Event Advisories	• None • Sources: ISMP, FDA, TJC

Look-alike / Sound-alike Error Potential	**NME Drug Name**	**Lexi-Comp**	**First DataBank**	**ISMP**	**Clinical Judgment**

Azelaic acid topical foam 15%	None	None	None	Acetic acid Azelastine AZILECT AZELEX cream
FINACEA	None	None	None	Finasteride ORACEA

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Severity of Rosacea	• The two major efficacy-safety trials included patients with *moderate to severe* PP rosacea (with the majority [86.8%–90.0%] having moderate disease); however, the FDA approved azelaic acid foam for treatment of *mild to moderate* PP rosacea.
Potential Advantages of Foam Formulation	• The authors of the phase II study noted that, in general, patients often prefer foam over other vehicles such as gel or cream because of the ease of spreadability and application, fast drying time, lower density, and lower likelihood of residue and/or odor remaining at the application site.[14] • In general, usability, spreadability, absorbability and emolliency appear to be the main advantages of a hydrophilic emulsion foam.[20] • The foam and gel formulations of azelaic acid have not been compared in a clinical study.
Patents and Exclusivities	• Azelaic acid is available as FINACEA topical gel 15%, which has a patent that expires in November 2018 and which has no unexpired exclusivities. • A generic azelaic acid gel (15%) product is tentatively approved and is not yet marketed. • FINACEA topical aerosol foam 15% has multiple patents expiring as early as September 2019 and at the latest January 2029.
Pipeline Drugs	• Numerous agents for different subtypes of rosacea are in various stages of development: AC-701, ACUD-1, DLX-1008, DMT-200, DMT-210, DMT-220, FMX-103, incobotulinumtoxin A, itraconazole, minocycline, omiganan pentahydrochloride, oxymetazoline hydrochloride, PAC-14028, DI-320 and tetracycline MR
Storage and Handling	• Azelaic acid foam should be stored at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). • WARNING: Flammable. Need to avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Must not puncture or incinerate. Must not expose to heat or store at temperatures above 120°F (49°C).

Dosing and Administration

- Apply azelaic acid foam twice daily (morning and evening) to the entire facial area (cheeks, chin, forehead, and nose). For a single application, dispense the smallest amount of foam necessary to adequately cover the affected area(s) with a thin layer.
- Shake well before use.
- Cosmetics may be applied after the application of azelaic acid foam has dried.
- Avoid the use of occlusive dressings or wrappings.
- Azelaic acid foam should be used continuously over 12 weeks.
- Reassess patients if no improvement is observed upon completing 12 weeks of therapy.
- Not for oral, ophthalmic or intravaginal use.

Special Populations (Adults)	
Elderly	• No overall differences in safety or effectiveness were observed between elderly (≥ 65 years) and younger study patients.
Pregnancy	• Pregnancy category B. • No adequate and well-controlled studies in pregnant women. Weigh risks versus benefits. • Embryotoxic in animals.
Lactation	• No well-controlled studies in nursing women. Weigh risks versus benefits.
Renal Impairment	• No guidance in prescribing information.
Hepatic Impairment	• No guidance in prescribing information.
Pharmacogenetics/genomics	• No data.

Projected Place in Therapy

- Rosacea is a common chronic inflammatory skin disorder primarily affecting the central aspects of the face (midforehead, nose, chin and cheeks). There are four subtypes: erythematotelangiectatic, papulopustular, phymatous and ocular rosacea. Rosacea is estimated to affect over 16 million people in the US,[21] with a prevalence ranging from 1% to 10% in fair-skinned populations.[22] Women are more commonly afflicted than men, and fair-skinned people (skin phototypes I and II, particularly those of Celtic and Northern European origin) are more likely to develop rosacea than dark-skinned individuals. Symptoms consist of flushing (transient erythema), nontransient erythema, telangiectasia, acne-like papules and/or pustules and possibly watery, irritated or bloodshot eyes (ocular rosacea). Men are more likely to develop distorting, skin thickening (phymatous) changes due to sebaceous overgrowth, particularly of the nose (rhinophyma). A barrier defect causes the skin to be sensitive and irritable. Dermal symptoms may vary in intensity over time; however, ocular rosacea tends to be consistent. The cause of rosacea is unknown but may involve dysfunctional cathelicidin antimicrobial and proinflammatory peptides, *Demodex folliculorum* mites carrying *Bacillus oleronius*, and vascular instability.[25] These factors may lead to a hyperactive innate immune system, release of inflammatory mediators, neutrophil release of reactive oxygen species, and damaged elastic fibers in the skin. Factors that may trigger rosacea include sunlight, emotional stress, hot weather, wind, heavy exercise, alcohol consumption and hot baths. Rosacea is not fatal, but because of its effects on a person's appearance, it can have a substantial negative effect on a person's self-confidence, social life, work attendance and quality of life.
- Therapy of rosacea should be selected based on the disease subtype (or combination of subtypes), severity of symptoms, response to previous treatments, tolerability, and patient expectations (such as rapid treatment effects). Education, skin care and treatment serve as the foundation of rosacea therapy. The following list summarizes pharmacologic treatment recommendations for rosacea, with a focus on azelaic acid:
    - Both the National Rosacea Society (NRS)[23] and the American Acne and Rosacea Society (AARS)[24] base treatment selection on disease classification and consider topical azelaic acid (or topical metronidazole) to be a first-line choice for initial therapy of mild or moderate PP rosacea.
    - UptoDate also suggests topical azelaic acid (or metronidazole) for mild to moderate PP rosacea, with topical ivermectin and topical sodium sulfacetamide as alternatives.[2] Topical metronidazole may be preferred over topical azelaic acid based on lower cost and lower risk for early skin irritation, particularly in patients with pronounced facial sensitivity.
    - The Rosacea International Expert (ROSIE) Group, on the other hand, based treatment selection on signs and symptoms, although these treatment recommendations from 2011 preceded those discussed above.[25] Within each signs and symptoms category, the severity could range from mild to severe. The ROSIE Group recommended topical azelaic acid (or topical metronidazole, topical sulfacetamide-sulfur, topical clindamycin or topical retinoid) alone or in combination with subantimicrobial doxycycline or short-term oral antibiotics for treatment of papules and pustules. Topical azelaic acid (or topical metronidazole, topical antibiotic, or topical retinoid) was also recommended in combination with oral antibiotics, oral isotretinoin or intralesional corticosteroids for treatment of nodules and plaques of rosacea.
- Based on the body of evidence, azelaic acid topical foam would provide benefit for reducing inflammatory lesions in patients with mainly moderate PP rosacea and may be used as an alternative to azelaic acid gel 15%, with consideration given to relative product costs and patient expectations and preferences. The treatment recommendations noted above suggest that azelaic acid is first-line therapy and may be useful in combination

with either other topical agents or oral agents, although the foam product has not been evaluated in combination regimens.

- Overall, a high-quality body of evidence suggests that azelaic acid topical foam has a small benefit over vehicle foam in achieving investigator-assessed global treatment success, reducing inflammatory lesion count and reducing erythema. While azelaic acid foam improved inflammatory lesions, it had no additional benefit over vehicle foam in terms of improving telangiectasia and a marginal benefit in improving quality of life. Substantial improvements were seen with vehicle foam, likely due to the beneficial effects of skin care. The clinical trial populations did not represent US Veterans, so there is some uncertainty about the extent to which the treatment effects will be experienced in VHA patients.

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Appendix A: GRADEing the Evidence

Quality of Evidence	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of theevidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.