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Azelaic Acid Topical Formulations: Differentiation of 15% Gel and 15% Foam

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Abstract

In this article, the author reviews topical formulations of azelaic acid used to treat papulopustular rosacea. Emphasis is placed on differences in vehicle technology and potential clinical impact of the possibility for neurosensory cutaneous tolerability reactions.

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Azelaic acid (AzA) is a medium chain dicarboxylic acid produced naturally by the commensal yeast, *Malassezia furfur*, which is part of the normal skin flora of humans and many other animals.[1,2] Found normally in low levels systemically in humans, ingestion of many food sources, such as wheat, barley, and rye, regularly expose people to AzA through dietary intake.[1–4] Available data show that AzA appears to be devoid of acute or chronic toxicity, is not mutagenic, and is not teratogenic. Additionally, no systemic safety signals have been associated with application of 20% cream, 15% gel, and/or 15% foam formulations; all three formulations have been extensively studied in research trials and collectively have been available in the United States marketplace for approximately 2.5 decades.[5–13]

Azelaic acid has been shown to exhibit several pharmacologic effects, which may correlate with clinical use in dermatology. A variety of anti-inflammatory and antioxidant properties have been reported, the former including downregulation of cathelicidin (LL-37) activation via inhibition of serine protease (kallikrein-5).[14–23] At least some of these effects are believed to correlate with therapeutic activity in papulopustular rosacea (PPR) and possibly acne vulgaris (AV).[14,20,21,23]

The majority of clinical studies with AzA are in adult patients treated for PPR utilizing either AzA 15% gel or AzA 15% foam.[3–13] AzA 20% cream is approved by the US Food and Drug Administration (FDA) for treatment of AV; however, interestingly, *in vitro* skin penetration data has shown that the cutaneous penetration and permeation of AzA is markedly greater after application of AzA 15% gel as compared to AzA 20% cream.[3,24–26] Both AzA 15% gel and AzA 15% foam are FDA approved for the treatment of PPR in adult patients with efficacy and safety both well-established in multiple studies.[3,4,13–20,27,28]

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WHAT ARE THE CONSTITUENT DIFFERENCES IN FORMULATION BETWEEN AzA 15% GEL AND AzA 15% FOAM AND HOW MAY THESE DIFFERENCES BE RELEVANT IN THE CLINICAL SETTING?

From a formulation perspective, brand AzA 15 % gel (Finacea Gel, Bayer HealthCare Pharmaceuticals) is an aqueous-based opaque vehicle; each gram contains 0.15g of AzA (active; 15% w/w), benzoic acid (preservative), disodium EDTA (chelating agent), lecithin (thickening agent), medium-chain triglycerides (lipid emollient), polyacrylic acid (emulsifying and suspending agent; penetration enhancer), polysorbate 80 (emulsifier), propylene glycol (humectant [low concentration]), purified water (base diluent), and sodium hydroxide (pH adjuster).[27]

The brand AzA 15% foam (Finacea Foam, Bayer HealthCare Pharmaceuticals) is formulated within its aluminum canister as a hydrophilic oil-in-water (o/w) emulsion pressurized with propellants (propane, butane, isobutane), converted to a foam upon release via a continuous spray valve; each gram contains 0.15g of AzA (active; 15% w/w), benzoic acid, (preservative), cetostearyl alcohol (emollient), dimethyl isosorbide (solvent/dispersant), medium-chain triglycerides (lipid [oil] phase emollient), methylcellulose (thickening agent), monoglycerides (lipid [oil] phase diluent), diglycerides (lipid [oil] phase diluent), polyoxyl 40 stearate (emulsifier), polysorbate 80 (emulsifier), propylene glycol (humectant [low concentration]), purified water (base diluent), sodium hydroxide (pH adjuster), and xanthum gum (thickening agent).[28] Many of the components of the foam vehicle support lipid-based emolliency, which may translate to a favorable skin tolerability profile. This is especially pertinent in rosacea-affected skin, where proper skin care has been shown to reduce sensory symptom-type side effects (e.g., stinging, burning, tingling) that can occur in a subset of rosacea patients treated with AzA 15% gel.[4,27,29–31]

Both AzA 15% gel and AzA 15% foam are FDA approved for the treatment of PPR in adults with efficacy established; however, no head-to-head comparison studies between these two formulations of AzA have been performed. Based on the similarity of study protocols, PPR populations enrolled in the pivotal trials, and therapeutic outcomes, clinically meaningful differences between AzA 15% gel and AzA 15% foam do not appear to be based on efficacy in rosacea.[4,6,7,27,28] Differentiation of the foam vehicle of AzA as compared to the gel formulation is more dependent on other vehicle-related factors that are directly relevant to the clinical setting. These include:

- Preference for one vehicle over another by a given patient may augment adherence with treatment, which could lead to a better therapeutic outcome. As both the AzA 15% gel and AzA 15% foam vehicles are aqueous-based and easily applied to facial skin, individual patients may favor one particular vehicle over another. Some patients established initially on AzA 15% gel may be interested in trying the foam vehicle, especially if they experience any adverse neurosensory symptoms after application, even if mild and/or transient (see below).
- More favorable cutaneous tolerability with an apparent decrease in adverse neurosensory symptoms (e.g., stinging, burning, tingling). The availability of the newer foam vehicle provides an option other than the gel. Although persistent/moderate-severe adverse neurosensory symptoms at the application site are uncommon with both the gel and the foam, assessment of available data suggest that these adverse effects may be less frequent with the foam.

WHAT INFORMATION IS AVAILABLE ON NEUROSENSORY CUTANEOUS TOLERABILITY WITH THE AzA 15% GEL AND AzA 15% FOAM VEHICLES AND CAN ANY POTENTIAL CONCLUSIONS BE GLEANED FROM THE DATA THAT IS RELEVANT TO CLINICIANS?

Before drawing definitive conclusions about treatment outcome differences between AzA 15% gel and AzA 15% foam, it is important to clarify that no head-to-head studies exist comparing these formulations. What can be pointed out is that the pivotal trials with both included adult subjects with facial PPR treated with either Aza 15% gel twice daily or AzA 15% foam twice daily versus their respective vehicles twice daily over a duration of 12 weeks.[4,6,7,27,28] Baseline demographics and disease-related characteristics were similar in the Phase 3 randomized controlled trials (RCTs) with both AzA 15% gel and AzA 15% foam and are depicted here:

- **Aza 15% gel.** Adults with PPR ≥18 years of age (mean age 48 years); predominantly moderate severity PPR by Investigator Global Assessment (IGA); standard exclusion and washout period criteria; 92.5 percent Caucasian skin; 73 percent women; mean baseline inflammatory lesion counts 17.5 to 17.8.[4]
- **AzA 15% foam.** Adults with PPR

≥18 years of age (mean age 51.2–51.9 years); predominantly moderate severity PPR by IGA; standard exclusion and washout period criteria; 95 percent white skin; 73 percent women; mean baseline inflammatory lesion counts 21.2 to 21.7.7.

Neurosensory cutaneous adverse events (AEs), such as stinging, burning, and tingling, and in some cases pruritus, are reported to be associated with topical application of AzA, distinct from visible tolerability reactions that produce dermatitis-type changes after topical application of many different products.[4-7,27,28,30,31] As the Phase 3 RCTs with AzA 15% gel did not incorporate skin care recommendations, there is the potential that this factor may have contributed at least partially to the apparent high rate of such skin tolerability-related AEs in the pivotal RCTs, even though most were transient and not severe.[4,27,29]

- **AzA 15% gel neurosensory skin tolerability.** In two Phase 3 RCTs of 12-weeks duration completed in the United States, the tolerability and safety were evaluated in subjects who used AzA 15% gel twice daily (n=333) or the gel vehicle twice daily (n=331) for PPR in adults.[4,27] In both trials, the most frequently reported treatment-related AEs were burning, stinging, and/or tingling (29%) and pruritus (11%), with all being predominantly transient and without the need to withdraw from therapy; 0.6% were noted to experience severe stinging and burning. Treatment was discontinued due to AEs in five percent of study subjects overall. The neurosensory AEs were markedly lower in the vehicle arms suggesting that the active ingredient is a key contributor to these reactions in a subset of subjects. Nevertheless, mitigation of these AEs with use of gentle skin care in many patients suggests that formulation characteristics may be adjusted to ameliorate these effects.[25,29,31]
- **AzA 15% foam neurosensory skin tolerability.** In two 12-week pivotal RCTs (Phase 2 and Phase 3 trials), AzA 15% foam twice daily (n=681) was evaluated in adults with PPR versus vehicle foam twice daily (n=681).[6,7,28] In both trials, application site "pain," a term required more recently in pivotal RCTs that includes stinging/burning/paresthesia/tenderness, occurred as a treatment-related AE in 6.2 percent, and pruritus in 2.5 percent of subjects. In the Phase 3 RCT completed with AzA 15% foam (n=484), application site "pain" occurred in 3.5 percent of AzA-treated subjects and pruritus in 1.4 percent of AzA-treated subjects; treatment was discontinued in 1.2 percent of AzA-treated subjects due to AEs; subjects were encouraged to use gentle skin care products although no specific products were supplied.[7]

Summary on neurocutaneous skin tolerability. The available data from RCTs on neurosensory skin symptomatology that occurs in a subset of individuals after use of either AzA 15% gel or AzA 15% foam, although not obtained from head-to-head studies, suggests that these AEs appear to potentially be less likely to occur with the AzA 15% foam vehicle. Data on gentle skin care have also supported that neurosensory AEs that occur in some individuals treated with AzA 15% gel are reduced when proper skin care is incorporated.[29,31] Collectively, these data support the importance of maintaining skin barrier integrity through incorporation of both proper skin care and advances in vehicle formulation technology.

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