

AZELAIC ACID- azelaic acid gel
Amneal Pharmaceuticals of New York LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AZELAIC ACID GEL safely and effectively. See full prescribing information for AZELAIC ACID GEL.

AZELAIC ACID gel, for topical use

Initial U.S. Approval: 1995

----- **RECENT MAJOR CHANGES** -----

Warnings and Precautions: Exacerbation of Asthma (5.4) 08/2016

----- **INDICATIONS AND USAGE** -----

Azelaic Acid Gel, 15% is indicated for topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. Efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Apply a thin layer of Azelaic Acid Gel, 15% twice daily to affected area(s). (2)
- Use only very mild soaps or soapless cleansing lotion before applying Azelaic Acid Gel, 15%. (2)
- Cosmetics may be applied after the application of Azelaic Acid Gel, 15% has dried. (2)
- Avoid spicy foods, thermally hot foods and drinks, alcoholic beverages. (2)
- Not for oral, ophthalmic or intravaginal use. (2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Gel, 15% (3)

----- **CONTRAINDICATIONS** -----

None. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- *Hypersensitivity*: In case of known hypersensitivity to any component of the gel, avoid the use of Azelaic Acid Gel, 15%. If hypersensitivity develops during treatment, discontinue Azelaic Acid Gel, 15% and institute appropriate therapy. (5.1)
- *Skin Reactions*: Skin irritation (i.e. pruritus, burning or stinging) may occur, usually during the first few weeks of treatment with Azelaic Acid Gel, 15%. If sensitivity or severe irritation develops and persists, discontinue treatment and institute appropriate therapy. (5.2)
- *Hypopigmentation*: Isolated cases of hypopigmentation occurred after azelaic acid use. Monitor patients with dark complexion for early signs of hypopigmentation (5.2)
- *Eye and Mucous Membrane Irritation*: Azelaic Acid Gel, 15% has been reported to cause irritation of the eyes. Therefore, avoid contact with the eyes and mucous membranes. (5.3)
- *Exacerbation of Asthma*: Consult a physician if asthma is exacerbated with Azelaic Acid Gel, 15% use. (5.4)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions are burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2019

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Azelaic Acid Gel, 15% is indicated for topical treatment of the inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

2 DOSAGE AND ADMINISTRATION

- Apply and gently massage a thin layer of Azelaic Acid Gel, 15% into the affected areas on the face twice daily (morning and evening).
- Use only very mild soaps or soapless cleansing lotion before application of Azelaic Acid Gel, 15%.
- Cosmetics may be applied after the application of Azelaic Acid Gel, 15% has dried.
- Avoid the use of occlusive dressings or wrappings.
- Instruct patients to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages.
- Patients should be reassessed if no improvement is observed upon completing 12 weeks of therapy.
- Not for oral, ophthalmic or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Azelaic Acid Gel, 15% is a white to yellowish white opaque gel. Each gram of Azelaic Acid Gel, 15% contains 0.15 gm of azelaic acid (15% w/w).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including cases of angioedema, eye swelling, facial swelling, dyspnea, urticaria, and adverse skin reactions, have been reported during post marketing surveillance.

Avoid the use of Azelaic Acid Gel, 15% in patients with known hypersensitivity to any component of the gel. If hypersensitivity develops during treatment, discontinue Azelaic Acid Gel, 15% and institute appropriate therapy.

5.2 Skin Reactions

Skin irritation (i.e. pruritus, burning or stinging) may occur during use of Azelaic Acid Gel, 15%, usually during the first few weeks of treatment. If sensitivity or severe irritation develops and persists, discontinue treatment and institute appropriate therapy.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, monitor these patients for early signs of hypopigmentation.

5.3 Eye and Mucous Membranes Irritation

Avoid contact with the eyes, mouth and other mucous membranes. If Azelaic Acid Gel, 15% does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists [see *Adverse Reactions (6.2)*].

5.4 Exacerbation of Asthma

Worsening of asthma has been reported in patients using azelaic acid formulations including Azelaic Acid Gel, 15%. Consult a physician if asthma is exacerbated with use of Azelaic Acid Gel, 15%.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two vehicle-controlled and one active-controlled U.S. clinical trials, treatment safety was monitored in 788 subjects who used twice-daily Azelaic Acid Gel, 15% for 12 weeks (N=333) or 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks. In all three trials, the most common treatment-related adverse events were: burning/stinging/tingling (29%), pruritus (11%), scaling/dry skin/xerosis (8%) and erythema/irritation (4%). In the active-controlled trial, overall adverse reactions (including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness) were 19.4% (24/124) for Azelaic Acid Gel, 15% compared to 7.1% (9/127) for the active comparator gel at 15

weeks.

Table 1: Adverse Events Occurring in $\geq 1\%$ of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

	Azelaic Acid Gel, 15% N=457 (100%)			Vehicle N=331 (100%)		
	Mild N=99 (22%)	Moderate N=61 (13%)	Severe N=27 (6%)	Mild N=46 (14%)	Moderate N=30 (9%)	Severe N=5 (2%)
Burning/stinging/tingling	71 (16%)	42 (9%)	17 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	29 (6%)	18 (4%)	5 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/dry skin/xerosis	21 (5%)	10 (2%)	5 (1%)	31 (9%)	14 (4%)	1 (<1%)
Erythema/irritation	6 (1%)	7 (2%)	2 (<1%)	8 (2%)	4 (1%)	2 (1%)
Contact dermatitis	2 (<1%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Edema	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Acne	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

*Subjects may have > 1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event.

In patients using azelaic acid formulations, the following adverse events have been reported: worsening of asthma, vitiligo, depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris) and exacerbation of recurrent herpes labialis.

Local Tolerability Studies

Azelaic Acid Gel, 15% and its vehicle caused irritant reactions at the application site in human dermal safety studies. Azelaic Acid Gel, 15% caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical trials, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

6.2 Post-Marketing Experience

The following adverse reactions have been identified post approval of Azelaic Acid Gel, 15%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure:

Eyes: iridocyclitis upon accidental exposure of the eyes to Azelaic Acid Gel, 15%

Hypersensitivity: angioedema, eye swelling, facial swelling, urticaria.

Respiratory: worsening of asthma, dyspnea, wheezing

7 DRUG INTERACTIONS

There have been no formal studies of the interaction of Azelaic Acid Gel, 15% with other drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Therefore, Azelaic Acid Gel,

15% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15% gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day [162 times the maximum recommended human dose (MRHD) based on body surface area (BSA)], rabbits given 150 or 500 mg/kg/day (19 or 65 times the MRHD based on BSA) and cynomolgus monkeys given 500 mg/kg/day (65 times the MRHD based on BSA) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose of 2500 mg/kg/day (162 times the MRHD based on BSA) that generated some maternal toxicity. In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the MRHD based on BSA). No effects on sexual maturation of the fetuses were noted in this study.

8.3 Nursing Mothers

It is not known whether azelaic acid is excreted in human milk; however, *in vitro* studies using equilibrium dialysis were conducted to assess the potential for human milk partitioning. The studies demonstrated that, at an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0. These data indicate that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of 20% azelaic acid cream is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. Nevertheless, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

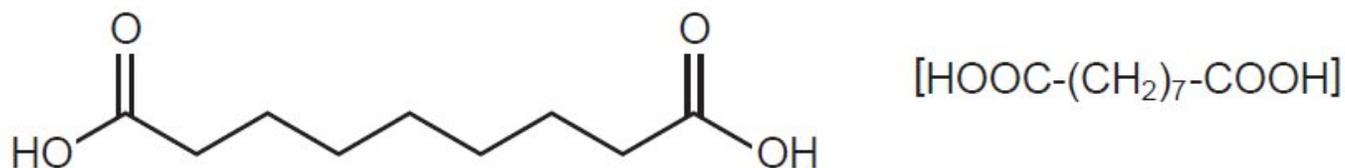
Safety and effectiveness of Azelaic Acid Gel, 15% in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Azelaic Acid Gel, 15% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Azelaic Acid Gel, 15%, is an aqueous gel which contains azelaic acid, a naturally-occurring saturated dicarboxylic acid. Chemically, azelaic acid is 1,7-heptanedicarboxylic acid. The molecular formula for azelaic acid is C₉H₁₆O₄. It has the following structure:



Azelaic acid has a molecular weight of 188.22. It is a white, odorless crystalline solid. It is poorly soluble in water at 20°C (0.24%) but freely soluble in boiling water and in ethanol.

Azelaic Acid Gel, 15% is a white to yellowish white opaque gel for topical use; each gram contains 0.15 gm azelaic acid (15% w/w) in an aqueous gel base containing benzoic acid (as a preservative), caprylic/capric triglycerides, carbopol 980, edetate disodium, polysorbate 80, propylene glycol, purified water, and sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which azelaic acid interferes with the pathogenic events in rosacea are unknown.

12.2 Pharmacodynamics

The pharmacodynamics of azelaic acid in association with the treatment of rosacea are unknown.

12.3 Pharmacokinetics

The percutaneous absorption of azelaic acid after topical application of Azelaic Acid Gel, 15% could not be reliably determined. Mean plasma azelaic acid concentrations in rosacea subjects treated with Azelaic Acid Gel, 15% twice daily for at least 8 weeks are in the range of 42 to 63.1 ng/mL. These values are within the maximum concentration range of 24.0 to 90.5 ng/mL observed in rosacea subjects treated with vehicle only. This indicates that Azelaic Acid Gel, 15% does not increase plasma azelaic acid concentration beyond the range derived from nutrition and endogenous metabolism.

In vitro and human data suggest negligible cutaneous metabolism of ³H-azelaic acid after topical application of 20% azelaic acid cream. Azelaic acid is mainly excreted unchanged in the urine, but undergoes some β -oxidation to shorter chain dicarboxylic acids.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (Tg.AC) mice, Azelaic Acid Gel, 15% and the gel vehicle, when applied once or twice daily, did not increase the number of female Tg.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male Tg.AC animals after once daily application. After twice daily application, Azelaic Acid Gel, 15% and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Azelaic acid was not mutagenic or clastogenic in a battery of *in vitro* [Ames assay, HGPRT in V79 cells (Chinese hamster lung cells), and chromosomal aberration assay in human lymphocytes] and *in vivo* (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the MRHD based on BSA) did not affect fertility or reproductive performance in male or female rats.

14 CLINICAL STUDIES

Azelaic Acid Gel, 15% was evaluated for the treatment of mild to moderate papulopustular rosacea in two multicenter, randomized, double-blind, vehicle-controlled, 12-week clinical trials having identical protocols and involving a total of 664 (active: 333; vehicle: 331) subjects aged 21 to 86 years (mean age = 49). Overall, 92.5% of subjects were Caucasian and 73% of subjects were female. Enrolled subjects had mild to moderate rosacea with a mean lesion count of 18 (range 8 to 60) inflammatory papules and

pustules. The following subjects were excluded: a) those without papules and pustules; b) those with nodules, rhinophyma, or ocular involvement and c) those with a history of hypersensitivity to propylene glycol or to any other ingredients of the study drug. Azelaic Acid Gel, 15% or its vehicle were to be applied twice daily for 12 weeks; no other topical or systemic medication affecting the course of rosacea and/or evaluability was to be used during the studies. Subjects were instructed to avoid spicy foods, thermally hot food/drink and alcoholic beverages during the study. Subjects were also instructed to use only very mild soaps or soapless cleansing lotion for facial cleansing.

The primary efficacy endpoints included both 1) change from baseline in inflammatory lesion counts as well as 2) success defined as a score of “clear” or “minimal” with at least a 2-step reduction from baseline on the Investigator’s Global Assessment (IGA), defined as follows below:

CLEAR:

No papules and/or pustules; no or residual erythema; no or mild to moderate telangiectasia

MINIMAL:

Rare papules and/or pustules; residual to mild erythema; mild to moderate telangiectasia

MILD:

Few papules and/or pustules; mild erythema; mild to moderate telangiectasia

MILD TO MODERATE:

Distinct number of papules and/or pustules; mild to moderate erythema; mild to moderate telangiectasia

MODERATE:

Pronounced number of papules and/or pustules; moderate erythema; mild to moderate telangiectasia

MODERATE TO SEVERE:

Many papules and/or pustules, occasionally with large inflamed lesions; moderate erythema; moderate degree of telangiectasia

SEVERE:

Numerous papules and/or pustules, occasionally with confluent areas of inflamed lesions; moderate or severe erythema; moderate or severe telangiectasia

Primary efficacy assessment was based on the “intent-to-treat” (ITT) population with the “last observation carried forward” (LOCF).

Both trials demonstrated a statistically significant difference in favor of Azelaic Acid Gel, 15% over its vehicle in both reducing the number of inflammatory papules and pustules associated with rosacea (Table 2) as well as demonstrating success on the IGA in the ITT-LOCF population at the end of treatment.

Table 2: Inflammatory Papules and Pustules (ITT population)*

	Study One Azelaic Acid Gel, 15% N=164	Study One VEHICLE N=165	Study Two Azelaic Acid Gel, 15% N=167	Study Two VEHICLE N=166
Mean Lesion Count Baseline	17.5	17.6	17.9	18.5
End of Treatment*	6.8	10.5	9.0	12.1
Mean Percent Reduction End of Treatment*	57.9%	39.9%	50.0%	38.2%

**ITT population with last observation carried forward (LOCF)*

Although some reduction of erythema which was present in subjects with papules and pustules of rosacea occurred in clinical trials, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

Azelaic Acid Gel, 15% was superior to the vehicle with regard to success based on the IGA of rosacea on a 7-point static score at the end of treatment (ITT population; Table 3).

Table 3: Investigator's Global Assessment at the End of Treatment*

	<u>Study One</u> Azelaic Acid Gel, 15% N=164	<u>Study One</u> VEHICLE N=165	<u>Study Two</u> Azelaic Acid Gel, 15% N=167	<u>Study Two</u> VEHICLE N=166
Clear, Minimal or Mild at End of Treatment (% of Subjects)	61%	40%	61%	48%

**ITT population with last observation carried forward (LOCF)*

16 HOW SUPPLIED

16.1 How Supplied

Azelaic Acid Gel, 15% is a white to yellowish white opaque gel supplied in 50 g tubes (NDC 0115-1624-56).

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Inform patients using Azelaic Acid Gel, 15% of the following information and instructions:

- For external use only.
- Before applying Azelaic Acid Gel, 15%, cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel.
- Avoid use of alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
- Avoid contact with the eyes, mouth and other mucous membranes. If Azelaic Acid Gel, 15% does come in contact with the eyes, wash the eyes with large amounts of water and consult their healthcare providers if eye irritation persists.
- Wash hands immediately following application of Azelaic Acid Gel, 15%.
- Cosmetics may be applied after the application of Azelaic Acid Gel, 15% has dried.
- Avoid the use of occlusive dressings or wrappings.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of Azelaic Acid Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, or allergic reactions occur, discontinue use and consult your physician.
- If allergic reactions occur, discontinue use and consult their healthcare providers.
- Advise patients to report any worsening of asthma to their healthcare providers.
- Report abnormal changes in skin color to their healthcare providers.
- To help manage rosacea, avoid any triggers that may provoke erythema, flushing, and blushing. These triggers can include spicy and thermally hot food and drinks such as hot coffee, tea, or alcoholic beverages.

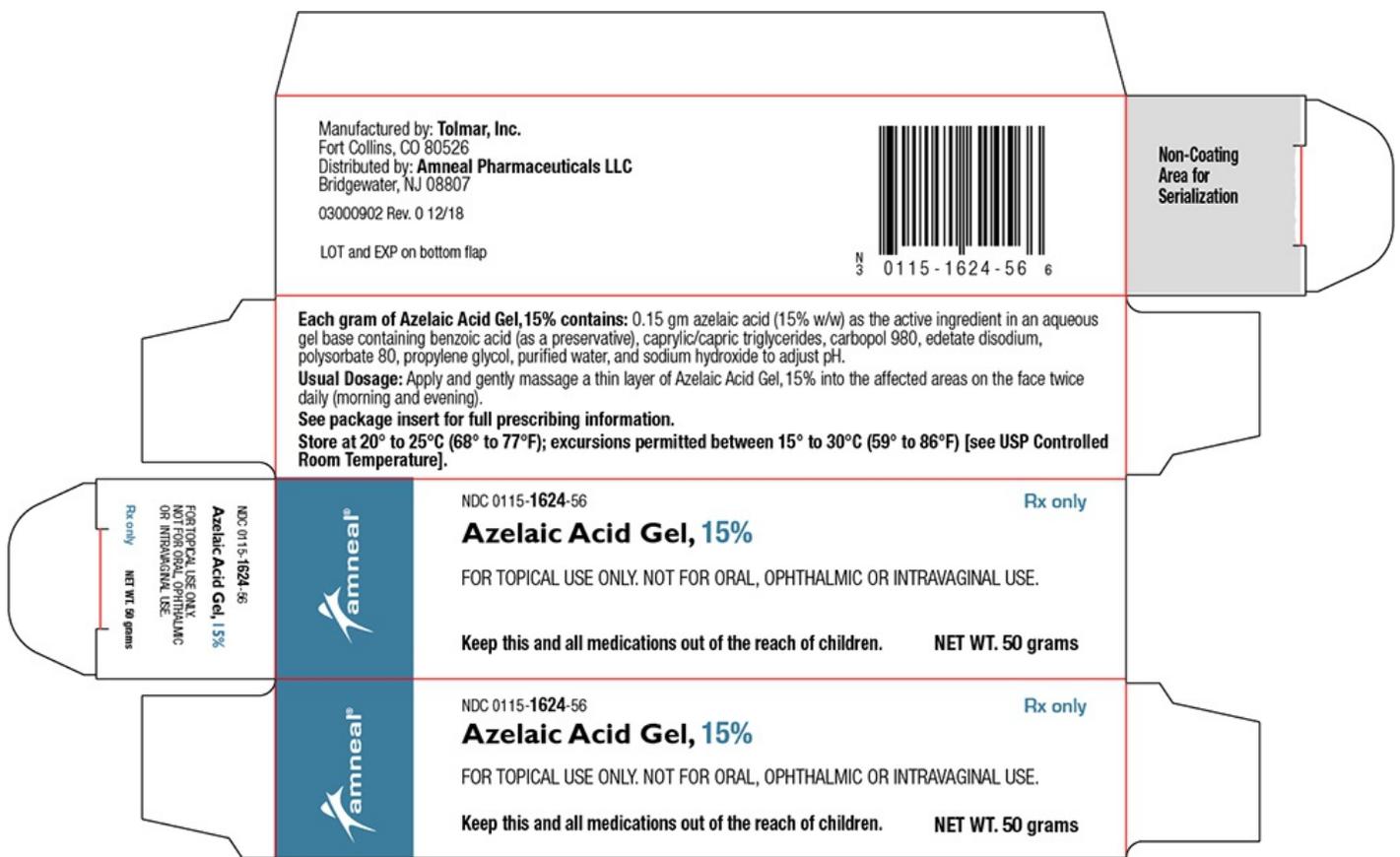
- Azelaic Acid Gel, 15% comes in a tube:
 - Tube instructions: Remove the cap before use. Squeeze the tube to dispense a small amount of Azelaic Acid Gel, 15%.

Manufactured by:
Tolmar, Inc.
 Fort Collins, CO 80526

Distributed by:
Amneal Pharmaceuticals LLC
 Bridgewater, NJ 08807

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PRINCIPAL DISPLAY PANEL



45g Carton Packaging

AZELAIC ACID

azelaic acid gel

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0115-1624
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AZELAIC ACID (UNII: F2VW3D43YT) (AZELAIC ACID - UNII:F2VW3D43YT)	AZELAIC ACID	0.15 g in 1 g

Inactive Ingredients

Ingredient Name	Strength
BENZOIC ACID (UNII: 8SKN0B0MIM)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	
CARBOMER HOMO POLYMER TYPE C (UNII: 4Q93RCW27E)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1624-56	1 in 1 CARTON	11/19/2018	
1		50 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA208724	11/19/2018	

Labeler - Amneal Pharmaceuticals of New York LLC (123797875)**Establishment**

Name	Address	ID/FEI	Business Operations
TOLMAR Inc.		791156578	ANALYSIS(0115-1624) , LABEL(0115-1624) , MANUFACTURE(0115-1624) , PACK(0115-1624)

Revised: 6/2019

Amneal Pharmaceuticals of New York LLC