

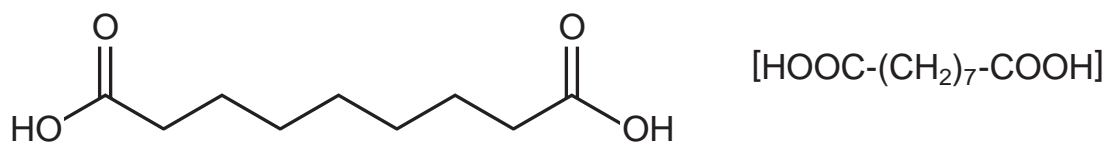


For Dermatologic Use Only—Not for Ophthalmic, Oral, or Intravaginal Use

Rx only

DESCRIPTION

FINACEA[®] (azelaic acid) Gel, 15%, contains azelaic acid, a naturally occurring saturated dicarboxylic acid. Chemically, azelaic acid is 1,7-heptanedicarboxylic acid, with the molecular formula C₉ H₁₆ O₄, a molecular weight of 188.22, and the structural formula:



Azelaic acid is a white, odorless crystalline solid that is poorly soluble in water at 20°C (0.24%), but freely soluble in boiling water and in ethanol.

Each gram of FINACEA Gel, 15%, contains 0.15 gm azelaic acid (15% w/w) as the active ingredient in an aqueous gel base containing benzoic acid (as a preservative), disodium-EDTA, lecithin, medium-chain triglycerides, polyacrylic acid, polysorbate 80, propylene glycol, purified water, and sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

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

Pharmacokinetics: The percutaneous absorption of azelaic acid after topical application of FINACEA Gel, 15%, could not be reliably determined. Mean plasma azelaic acid concentrations in rosacea patients treated with FINACEA 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 patients treated with vehicle only. This indicates that FINACEA 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 20% cream after topical application. Azelaic acid is mainly excreted unchanged in the urine, but undergoes some β-oxidation to shorter chain dicarboxylic acids.

CLINICAL STUDIES

FINACEA Gel, 15%, was evaluated for the treatment of mild to moderate papulopustular rosacea in 2 clinical trials comprising a total of 664 (333 active to 331 vehicle) patients. Both trials were multicenter, randomized, double-blind, vehicle-controlled 12-week studies with identical protocols. Overall, 92.5% of patients were Caucasian and 73% of patients were women, and the mean age was 49 (range 21 to 86) years. Enrolled patients had mild to moderate rosacea with a mean lesion count of 18 (range 8 to 60) inflammatory papules and pustules. Subjects without papules and pustules, with nodules, rhinophyma, or ocular involvement, and a history of hypersensitivity to propylene glycol or to any other ingredients of the study drug were excluded. FINACEA 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. Patients were instructed to avoid spicy foods, thermally hot foods and drinks, and alcoholic beverages during the study, and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

The primary efficacy endpoints were both 1) change from baseline in inflammatory lesion counts and 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):

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 last observation carried forward (LOCF).

Both studies demonstrated a statistically significant difference in favor of FINACEA[®] Gel, 15%, over its vehicle in reducing the number of inflammatory papules and pustules associated with rosacea (Table 1) and with success on the IGA in the ITT-LOCF population at the end of treatment.

Table 1. Inflammatory Papules and Pustules (ITT population)¹

	<u>Study One</u> FINACEA Gel,15% N = 164	<u>Study</u> <u>One</u> VEHICL E N = 165	<u>Study Two</u> FINACEA Gel, 15% N = 167	<u>Study</u> <u>Two</u> VEHIC LE N = 166
Mean Lesion Count Baseline	17.5	17.6	17.9	18.5
End of Treatment ¹	6.8	10.5	9.0	12.1
Mean Percent Reduction End of Treatment ¹	57.9%	39.9%	50.0%	38.2%

¹ITT population with last observation carried forward (LOCF);

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.

FINACEA Gel, 15%, was superior to the vehicle with regard to success based on the investigator's global assessment of rosacea on a 7-point static score at the end of treatment, (ITT population; Table 2).

Table 2. Investigator's Global Assessment at the End of Treatment¹

	<u>Study One</u> FINACEA Gel,15% N = 164	<u>Study One</u> VEHICLE N = 165	<u>Study Two</u> FINACEA Gel, 15% N = 167	<u>Study</u> <u>Two</u> VEHICLE N = 166
CLEAR, MINIMAL or MILD at End of Treatment (% of Patients)	61%	40%	61%	48%

¹ITT population with last observation carried forward (LOCF);

INDICATIONS AND USAGE

FINACEA Gel, 15%, is indicated for topical treatment of 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. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

CONTRAINDICATIONS

FINACEA Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS

FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravaginal use.

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, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS

General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA Gel, 15%, treatment should be discontinued and appropriate therapy instituted.

In a transgenic mouse study, chronic use of Finacea gel led to an increased number of animals with papillomas at the treatment site (**see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility**). The clinical relevance of the findings in animal studies to humans is not clear.

Information for Patients: Patients using FINACEA Gel, 15%, should receive the following information and instructions:

- FINACEA Gel, 15%, is to be used only as directed by the physician.
- FINACEA Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA-Gel, 15%. Avoid alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
- Avoid contact of FINACEA Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
- The hands should be washed following application of FINACEA Gel, 15%.
- Cosmetics may be applied after FINACEA Gel, 15%, has dried.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA Gel, 15%, should be discontinued, and patients should consult their physician (See **ADVERSE REACTIONS**).
- Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
- Patients should report abnormal changes in skin color to their physician.
- Avoid the use of occlusive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA[®] Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, 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, FINACEA 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, FINACEA 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 maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

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 based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) 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 that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). 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 maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers: Equilibrium dialysis was used to assess human milk partitioning *in vitro*. 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, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, 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. However, caution should be exercised when FINACEA Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA Gel, 15%, in pediatric patients have not been established.

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

ADVERSE REACTIONS

Overall, treatment related adverse events, including burning, stinging/tingling, dryness/tightness/ scaling, itching, and erythema/irritation/redness, were 19.4% (24/124) for FINACEA Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

	FINACEA 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.

FINACEA Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA 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 studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

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

Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA Gel, 15%, to the eye (see **PRECAUTIONS**).

OVERDOSAGE

FINACEA Gel, 15%, is intended for cutaneous use only. If pronounced local irritation occurs, patients should be directed to discontinue use and appropriate therapy should be instituted (See **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

A thin layer of FINACEA Gel, 15%, should be gently massaged into the affected areas on the face twice daily, in the morning and evening. Patients should be reassessed if no improvement is observed upon completing 12 weeks of therapy.

HOW SUPPLIED

FINACEA Gel, 15%, is supplied in tubes in the following size:

FINACEA Gel, 15% – 50 g tube – NDC 10922-825-02

Storage

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

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