

PRODUCT MONOGRAPH

Pr **FINACEA**[®]

Azelaic Acid Gel

15% w/w

Topical

Antirosacea Agent

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PrFINACEA®

Azelaic Acid Gel 15% w/w

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
topical	gel / 15% w/w	benzoic acid, disodium edetate, lecithin, medium-chain triglycerides, polyacrylic acid, polysorbate 80, propylene glycol, sodium hydroxide <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

FINACEA (azelaic acid gel) is indicated for:

- Topical treatment of inflammatory papules and pustules and erythema of mild to moderate rosacea.

CONTRAINDICATIONS

- FINACEA (azelaic acid gel) is contraindicated in individuals with a history of hypersensitivity to azelaic acid, propylene glycol or to any other component of the formulation. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

FINACEA (azelaic acid gel) should be used only as directed by a physician.

FINACEA is for dermatological use only, and not for ophthalmic, oral, rectal or intravaginal use.

Skin

FINACEA contains benzoic acid and propylene glycol which may cause mild irritant cutaneous and mucocutaneous reactions. Care should be taken to avoid contact with the eyes, mouth and other mucous membranes, and patients should be instructed accordingly. In the event of accidental contact, the eyes, mouth and/or affected mucous membranes should be washed with large amounts of water. If eye irritation persists, patients should consult a physician.

If pronounced local irritation occurs, patients should be directed to temporarily use the medication less frequently or to discontinue use for a few days. In case of sensitization, or if severe irritation persists, FINACEA should be discontinued and appropriate therapy instituted.

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

Carcinogenicity and Mutagenicity

Long-term animal studies have not been performed to evaluate the carcinogenic potential of FINACEA Gel. 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.

In a 26-week dermal carcinogenicity study using male and female transgenic (Tg.AC) mice, FINACEA and the gel vehicle did increase the number of papillomas in male animals after twice daily application at the treatment site. This effect was not observed after single administration in male and female mice. This effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear (see **TOXICOLOGY - Animal Toxicology**).

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.

Special Populations

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Therefore, FINACEA Gel 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. Embryofetal developmental studies with oral administration of azelaic acid to rats, rabbits, and cynomolgus monkeys during the period of organogenesis revealed embryotoxicity at doses where some maternal toxicity was noted. No teratogenic effects were observed. The embryofetal NOAEL was 32 times the MRHD based on BSA in rats, 6.5 times the MRHD based on BSA in rabbits and 19 times the MRHD based on BSA in monkeys.

In a peri- and post-natal developmental study in rats where azelaic acid was administered orally from gestational day 15 to through day 21 postpartum slight disturbances in the post-natal development of fetuses were noted at oral doses that generated some maternal toxicity. The NOAEL was 3 times the MRHD based on BSA. No effects on sexual maturation of the fetuses were noted in this study (see **TOXICOLOGY**).

Nursing Women

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 the drug into the maternal milk may occur. Since less than 4% of a topically applied dose 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 is administered to a nursing mother.

Pediatrics (< 18 years of age)

The safety and effectiveness of FINACEA in pediatric patients has not been established.

Geriatrics (> 65 years of age)

Clinical studies of FINACEA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Local skin irritation (mostly burning or itching sensations, occasionally reddening and scaling) may occur, usually at the start of treatment with FINACEA (azelaic acid gel). In the majority of cases, the irritation symptoms are mild and generally regress during the course of treatment. In very rare cases, allergic skin reactions (e.g., rash) may occur to azelaic acid or any of the nonmedicinal ingredients (see **CONTRAINDICATIONS**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In pivotal studies (two 12-week, vehicle-controlled clinical trials; n=664), safety was monitored in the 333 patients who used FINACEA and the 331 patients who used the gel vehicle.

Table 1: Cutaneous Adverse Events Occurring in 1% or More of Subjects in Two Clinical Trials in Rosacea Patients, by Treatment Group and Maximum Intensity*

	FINACEA n = 333 (100%)			Vehicle n = 331 (100%)		
	mild n = 86 (26%)	moderate n = 44 (13%)	severe n = 20 (6%)	mild n = 49 (15%)	moderate n = 27 (8%)	severe n = 5 (2%)
Cutaneous						
burning/stinging/tingling	66 (20%)	30 (9%)	12 (4%)	8 (2%)	6 (2%)	2 (1%)
pruritus	24 (7%)	14 (4%)	3 (1%)	9 (3%)	6 (2%)	0 (0%)
scaling/dry skin/xerosis	21 (6%)	8 (2%)	4 (1%)	33 (10%)	12 (4%)	1 (0%)
erythema/irritation	6 (2%)	6 (2%)	1 (0%)	8 (2%)	4 (1%)	2 (1%)
edema	3 (1%)	2 (1%)	1 (0%)	3 (1%)	0 (0%)	0 (0%)
contact dermatitis	2 (1%)	2 (1%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
acne	2 (1%)	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)
seborrhea	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
photosensitivity	1 (0%)	0 (0%)	0 (0%)	3 (1%)	1 (0%)	1 (0%)
skin disease	1 (0%)	0 (0%)	0 (0%)	1 (0%)	2 (1%)	0 (0%)

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

No phototoxicity or photoallergenicity was reported in the controlled clinical studies and in human dermal safety studies.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Cardiovascular: vasodilatation

Infections and Infestations: exacerbation of recurrent herpes labialis, herpes simplex and herpes zoster infections

Respiratory: worsening of asthma

Skin: acne flare, nevi, hirsutism, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), mycosis

Post-Market Adverse Drug Reactions

The following additional adverse reactions have been reported during post-approval use of FINACEA (frequency unknown):

- Hypersensitivity, which may occur with one or more of the following adverse reactions: angioedema, eye swelling, swelling face, dyspnoea
- Urticaria

DRUG INTERACTIONS

Overview

There have been no formal studies evaluating the interaction of FINACEA (azelaic acid gel) with other drugs.

The pivotal clinical trials excluded concomitant use of medications that affect rosacea.

Drug-Lifestyle Interactions

FINACEA (azelaic acid gel) has no influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

FINACEA (azelaic acid gel) is intended for topical use only.

Before application, the skin should be thoroughly washed and patted dry with a soft towel. Only very mild soaps or mild soapless cleansing lotions should be used.

A thin layer of FINACEA (0.5 g or approximately 2.5 cm of gel) should be applied twice daily, in the morning and evening, to the entire affected areas and gently massaged into the skin. The use of occlusive dressings or wrappings should be avoided, and the hands should be washed following application. During application, contact with the eyes should be avoided. In case of accidental exposure, the eyes should be rinsed with plenty of water.

It is important to use FINACEA continuously over the entire period of treatment.

In the event of skin irritation, the amount of gel per application should be reduced or the frequency of use of FINACEA should be decreased to once a day until the irritation ceases. If required, the treatment should be interrupted for a few days.

Avoid contact with the mouth, eyes and other mucous membranes. If FINACEA comes in contact with the eyes, wash with large amounts of water and consult a physician if eye irritation persists.

The hands should be washed after application of FINACEA.

The duration of use of FINACEA can vary from person to person and also depends on the severity of rosacea. Significant initial therapeutic effects have been observed after four to eight weeks of treatment.

Non-medicated cosmetics or cosmetics free of substances causing acniforme eruptions or irritations may be applied after the application of FINACEA has dried.

Patients should be instructed to avoid spicy foods, hot foods and drinks, and alcoholic beverages.

OVERDOSAGE

FINACEA (azelaic acid gel) is intended for cutaneous use only. If pronounced local irritation occurs due to excessive application, patients should be directed to temporarily use the medication less frequently or to discontinue use until symptoms and signs subside (See **WARNINGS AND PRECAUTIONS**).

Acute toxicology studies in laboratory animals do not indicate that acute intoxication is to be expected following oral ingestion of large amounts of the drug.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

While the pathophysiology of rosacea is not completely understood, there is increasing consensus that inflammation involving the elevation of several pro-inflammatory effector molecules such as kallikrein-5 and cathelicidin as well as reactive oxygen species (ROS), is a central process of this disease.

Azelaic acid has been shown to directly inhibit kallikrein-5 and cathelicidin expression in three models: *in vitro* (human keratinocytes), in murine skin and in the facial skin of patients with rosacea.

These anti-inflammatory properties of azelaic acid may play a role in the treatment of rosacea. While the clinical significance of these findings regarding kallikrein-5 and cathelicidin and their impact on the pathophysiology of rosacea has not yet been fully demonstrated in a large clinical study, initial studies in human facial skin appear to confirm the *in vitro* and murine findings.

Pharmacodynamics

Azelaic acid has been characterized as anti-keratinizing and anti-bacterial. The mechanisms by which azelaic acid interferes with the pathogenic events in rosacea are unknown, but appear to include an anti-inflammatory effect. *In vitro* findings indicate that azelaic acid inhibits the production and/or release of reactive pro-inflammatory oxygen species from neutrophils. The clinical relevance of this *in vitro* effect is unknown.

Pharmacokinetics

Metabolism

Azelaic acid is a dietary constituent (found in whole-grain cereals and animal products), and can be formed endogenously from longer-chain dicarboxylic acids, metabolism of oleic acid, and β -oxidation of monocarboxylic acids. Negligible cutaneous metabolism occurs after topical application.

Absorption

Endogenous plasma concentration (20 to 80 ng/mL) and daily urinary excretion (4 to 28 mg) of azelaic acid are highly dependent on dietary intake. The percutaneous absorption of azelaic acid after topical application of azelaic acid 15% gel is unknown. After topical application of an azelaic acid 20% cream, approximately 4% of azelaic acid is systemically absorbed. There was no difference between azelaic acid 15% gel and azelaic 20% cream in the urinary excretion of azelaic acid in patients with facial acne treated over a period of 8 weeks. Additionally, plasma azelaic acid concentrations in rosacea patients treated with FINACEA gel twice daily for at least 8 weeks are within the range of endogenous plasma azelaic acid concentrations. This indicates that FINACEA does not increase plasma azelaic acid concentration beyond the range derived from nutrition and endogenous metabolism.

Excretion

Azelaic acid is mainly excreted unchanged in the urine, but undergoes some β -oxidation to shorter-chain dicarboxylic acids. The observed half-lives in healthy subjects are approximately 45 minutes after oral dosing and 12 hours after topical dosing of the cream, indicating percutaneous absorption rate-limited kinetics.

STORAGE AND STABILITY

Store at room temperature (between 15°C and 30°C).

SPECIAL HANDLING INSTRUCTIONS

Keep out of the reach of children before and after use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FINACEA (azelaic acid gel) is available in tubes of 5 g and 50 g.^a Each tube is made of aluminum, with a membrane closure, an internal epoxide resin coating, a white exterior and a screw cap made of high-density polyethylene.

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

^a Not all presentations may be available in Canada.

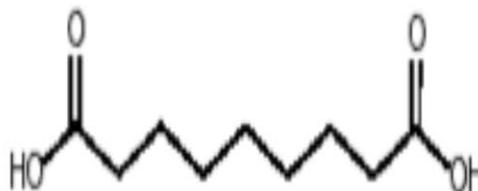
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	azelaic acid
Chemical name:	nonanedioic acid (IUPAC) 1,9-nonanedioic acid (CAS)
Molecular formula and molecular mass:	C ₉ H ₁₆ O ₄ 188.22

Structural formula:



Physicochemical properties:	Physical form: white, crystalline powder Melting point: 105°C to 110°C
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CLINICAL TRIALS

FINACEA was evaluated for the treatment of papulopustular rosacea in two pivotal efficacy studies comprising a total of 664 patients. Both studies were multicentre, randomized, double-blind, vehicle-controlled studies with identical protocols. Baseline eligibility criteria included moderate rosacea with 10 to 50 inflammatory papules and pustules, persistent erythema and telangiectasia. Subjects without papules and pustules, subjects with nodules, rhinophyma or ocular involvement, and subjects with a history of hypersensitivity to ingredients of the study drug were excluded. FINACEA 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 applied during the studies. Patients were instructed to avoid spicy foods, hot foods and drinks, and alcoholic beverages during the study, and only to use very mild soaps or soapless cleansing lotions on the face.

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 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 have demonstrated a statistically significant difference in favour of FINACEA Gel over its' vehicle in reducing the number of inflammatory papules and pustules associated with rosacea and with success on the IGA in the ITT-LOCF population at the end of treatment.

Study Demographics and Trial Design

Table 2: Summary of Patient Demographics for Clinical Trials in Rosacea

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Age range (mean)	Gender
1	double-blind, randomized, vehicle-controlled, parallel-group, multicentre	0.5 g (approx. 2.5 cm of gel) applied twice daily to the entire face topical 12 weeks	Finacea: 164 Vehicle: 165	21-84 (48.0) 24-77 (49.2)	40 M, 124 F 45 M, 120 F
2	double-blind, randomized, vehicle-controlled, parallel-group, multicentre	0.5 g (approx. 2.5 cm of gel) applied twice daily to the entire face topical 12 weeks	Finacea: 169 Vehicle: 166	24-86 (47.6) 23-78 (47.0)	48 M, 121 F 46 M, 120 F

Study Results

Table 3: Efficacy Results of Clinical Study 1

Primary Endpoints	FINACEA (n=164)	Vehicle (n=165)
Inflammatory papules and pustules (ITT population) ¹		
Mean lesion count		
Baseline	17.5	17.6
End of treatment ¹	6.8*	10.5
Mean percent reduction		
End of treatment ¹	58.1% ⁺	40.2%
Investigator's global assessment at the end of treatment ¹		
Clear, minimal or mild at end of treatment (% of patients)	61%*	40%

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

* statistically significant differences between FINACEA and vehicle $p < 0.0001$

+ statistically significant differences between FINACEA and vehicle with $p = 0.0001$

Table 4: Efficacy Results of Clinical Study 2

Primary Endpoints	FINACEA (n=169)	Vehicle (n=166)
<u>Inflammatory papules and pustules (ITT population)¹</u>		
Mean lesion count		
Baseline	17.8	18.5
End of treatment ¹	8.7*	11.8
Mean percent reduction		
End of treatment ¹	50.7% ⁺	38.7%
<u>Investigator's global assessment at the end of treatment¹</u>		
Treatment success (clear, minimal or mild) at end of treatment (% of patients)	62% ⁺⁺	48%

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

* statistically significant differences between FINACEA and vehicle $p = 0.0144$

+ statistically significant differences between FINACEA and vehicle with $p = 0.0208$

++ statistically significant differences between FINACEA and vehicle with $p = 0.0127$

FINACEA had a significantly greater effect than its vehicle in reducing the number of inflammatory papules and pustules associated with rosacea. Significant treatment differences

were discernible after four weeks; at the end of treatment (at last visit), FINACEA achieved mean reductions of 50.7% and 58.1% in the count of the inflammatory lesions.

Adverse events were monitored in patients who used FINACEA in the clinical studies. Treatment-emergent adverse events causally associated with FINACEA predominantly affected the skin. The most frequent cutaneous adverse events related to FINACEA and occurring in more than 10% of patients included burning, 21%, itching, 12%, and stinging, 12%. Events occurring in 1 to 10% of patients included dry skin, 9%, and rash, 4%. Other treatment-related cutaneous adverse events reported in less than 1% of patients during treatment with FINACEA included acne flare, contact dermatitis and facial edema. Single cases of hirsutism were reported with FINACEA and vehicle respectively; a relation to medication appears doubtful. The majority of adverse events were mild to moderate in severity. No phototoxicity or photoallergenicity was reported in the studies.

DETAILED PHARMACOLOGY

Pharmacodynamics

In vitro, azelaic acid was bacteriostatic and bactericidal against a variety of aerobic and anaerobic bacteria including *Propionibacterium acnes* and *Staphylococcus aureus*. The numbers of *P. acnes* are known to be elevated in acne vulgaris and successful antibacterial treatment of acne causes a decline in *P. acnes* populations.

The effects of azelaic acid on the accumulation of keratinous material in the infundibular region of the sebaceous follicle (the microcomedo) were tested in an in vivo animal model (tetradecane-induced comedo formation in the rabbit ear). A statistically significant reduction of follicular epithelial hyperplasia (i.e., comedo size) was observed morphometrically after daily application of an ethanolic solution containing 20% azelaic acid or after daily application of azelaic acid 20% cream for 11 days to rabbit ears pretreated with tetradecane. No effect was observed after similar application of ethanolic solution of 20% pimelic acid, the initial metabolite formed in animals and humans by β -oxidation, for 11 consecutive days.

To determine if azelaic acid has a direct effect on the sebaceous gland, an ethanolic solution containing 10% azelaic acid or a cream formulation containing 20% azelaic acid was applied to the ear and flank organ of intact male golden Syrian hamsters and to castrated, testosterone propionate-substituted golden Syrian hamsters. There were no effects on ear tissue lipid profiles, serum total cholesterol, triglycerides or fatty acids after daily application over four months.

Because of the higher water solubility of the disodium salt of azelaic acid, sodium azelinate was used to study the effects of azelaic acid on intermediary metabolism and its general pharmacological profile in vivo and in vitro.

In determining the effects of azelaic acid on intermediary metabolism, a single 1000 mg/kg intravenous dose of sodium azelinate in rats resulted in transient (15 to 30 minutes after dosing) increases in lactate concentration associated with reduced free fatty acid concentrations. In a similar study of rabbits dosed intravenously with 100 mg/kg/day of sodium azelinate for six consecutive days, glucose tolerance was slightly delayed, but there was no effect on liver function, plasma concentrations of lactate, pyruvate and glucose, and serum concentrations of urea and creatinine.

In general pharmacology studies of sodium azelinate, neurotropic effects observed in rats following a single intravenous administration were limited to individual instances of mydriasis (400 mg/kg) and slightly reduced locomotor activity (800 mg/kg) in the Irwin test. Sodium azelinate had no chronotropic or inotropic effects on spontaneous or stimulated contractions in isolated guinea pig atria preparations at concentrations up to 10^{-3} mol/L. However, a slight increase in spontaneous rate accompanied by a slight decrease in contractility was observed in the highest concentration tested (10^{-2} mol/L). In addition, sodium azelinate did not affect stimulated contraction of isolated guinea pig papillary muscle at similar concentrations. In conscious rats, intravenous administration of sodium azelinate at ascending doses of 10, 50 or 250 mg/kg did not influence heart rate or blood pressure up to one hour post-administration.

Renal function of Wistar rats (monitored by excretion of Na^+ , K^+ and Ca^{2+} , and urinary flow over a 20-hour period) was not affected after single intravenous doses of sodium azelinate (up to 1000 mg/kg).

Sodium azelinate had no clear effect on isolated smooth muscle preparations of guinea pig ileum, trachea or uterus with the exception of a moderate stimulatory effect at a very high in vitro concentration of 25 mg/mL.

Absorption, Distribution, Metabolism, Excretion

All studies of absorption, distribution, metabolism and excretion (ADME) were conducted using ^{14}C -labeled azelaic acid ($[^{14}\text{C}]\text{AzA}$). $[^{14}\text{C}]\text{AzA}$ contained the ^{14}C -label at both carboxyl groups and had a specific activity and a radiochemical purity of 4.136 GBq/mmol and > 97%, respectively. $[^{14}\text{C}]\text{AzA}$ was diluted with non-radiolabeled drug to the specific activity used in each experiment. Radioactivity was measured using liquid scintillation counting with quench monitoring and correction by the external standard ratio method. The bioanalytical methods employed for measurement of unchanged drug and its metabolites were high-performance liquid chromatography with radiochemical detection and liquid chromatography/ mass spectrometry / mass spectrometry (LC/MS/MS).

Because azelaic acid is a straight-chain dicarboxylic acid, it is expected that the main process of elimination is by biotransformation. Systemically absorbed azelaic acid is metabolized by β -oxidation into shorter straight-chain dicarboxylic acids (i.e., pimelic and glutaric acids), malonyl-CoA and acetyl-CoA. Released acetate enters the Krebs cycle for energy production or is used for lipid synthesis. Therefore, in these studies, exhaled ^{14}C -label ($^{14}\text{CO}_2$) indicates catabolism of the released acetate.

Absorption, distribution, metabolism and excretion studies of $[^{14}\text{C}]\text{AzA}$ were conducted in the same species used in toxicology studies (rats, rabbits, dogs and monkeys). For each species, both the oral (intra-gastric) and intravenous routes of administration were employed to investigate absorption and systemic bioavailability by following the time course of plasma levels, distribution into organs and tissues, and pathways and rates of excretion.

$[^{14}\text{C}]\text{AzA}$ was almost completely absorbed in rats, rabbits, dogs and monkeys when given as a single intra-gastric administration of a microcrystalline suspension at doses (1000 mg/kg in rats, 500 mg/kg in rabbits, 100 mg/kg in dogs and 150 mg/kg in monkeys) which were comparable to those used in toxicology studies. Across species, the label was excreted mainly in the urine.

After a single intra-gastric administration of 500 mg/kg to nonpregnant female rabbits or of 400 mg/kg to pregnant rabbits, the ^{14}C -label was excreted mainly in the urine (49% and 47%,

respectively), with only trace amounts of radioactivity (1.5% and approximately 0.5%, respectively) present in the feces. While only a trace amount of the administered radioactivity was able to pass the placental barrier, the relative amounts of radioactivity in the fetus and fetal liver were similar to those in the dam, indicating that azelaic acid and its metabolites did not accumulate in the fetus.

The ^{14}C -label was rapidly distributed throughout rat body tissues after a single intravenous dose of 10 mg/kg of [^{14}C]AzA. High levels of radioactivity were found in the kidney (the main organ of excretion) and in the liver, and trace amounts of radioactivity appeared to cross the blood-brain barrier (brain, spinal cord). No radioactivity was detected in the fetuses of pregnant rats given a single 10 mg/kg dose of [^{14}C]AzA intravenously. No differences in distribution pattern were observed between albino and pigmented rats. The ^{14}C -label was rapidly excreted (within 24 hours of injection) mainly with the urine (64%) and with respiratory air (18%). Only trace amounts of radioactivity (1.5%) were present in the feces.

Similarly, in rabbits given a single 10 mg/kg dose of [^{14}C]AzA intravenously, the ^{14}C -label was also rapidly excreted mainly with the urine (53% to 65%) and respiratory air (19%), with only trace amounts found in the feces (0.7%). In dogs given the same intravenous dose level, 64% of the label was excreted with the urine and 0.6% was excreted with the feces. Approximately equal amounts of the ^{14}C -label were excreted in the urine and in respiratory air of cynomolgus monkeys after a single intravenous dose of 10 mg/kg of [^{14}C]AzA, suggesting that azelaic acid may be metabolized to a greater extent in monkeys than in other animals.

In order to evaluate the effects of azelaic acid in animals after topical administration, studies of the percutaneous absorption of azelaic acid 20% cream and 15% gel were conducted in vitro in mice and in vivo in rats and dogs.

In an in vitro skin penetration model using hairless mouse skin, the gel formulation delivered a higher dose fraction (6% to 25%) into the skin than the cream formulation (3%), even though the average steady state percutaneous flux of [^{14}C]AzA was greater for the cream formulation (8.9 $\mu\text{g}/\text{cm}^2/\text{hr}$) than for the gel formulations (2.8 to 4.4 $\mu\text{g}/\text{cm}^2/\text{hr}$), suggesting a potential for lower systemic burden and higher drug concentration in viable skin for the gel formulation compared with the cream formulation. In rats and dogs, the in vivo percutaneous absorption of azelaic acid cream and gel formulations was compared. In rats, at the highest dose (300 mg/kg), the absorption of the cream formulation was almost two times higher than the gel (2.4% and 1.3%, respectively). In the dog, after a single dermal application of the 20% cream at either 34 mg/kg or 150 mg/kg, the percutaneous absorption was 0.24% and 1.16%, respectively. After a single dermal application of the gel formulation to dogs at 15 mg/kg or 150 mg/kg, the percutaneous absorption was 3.83% and 0.43%, respectively, corresponding to nearly identical percutaneous fluxes of 1.2-1.3 $\text{g}/\text{cm}^2/\text{hr}$ of azelaic acid. Since the treatment area was kept constant, the ten-fold dose increase was achieved by an increase in the thickness of the gel layer applied to the skin. The constant percutaneous flux, independent of the area dose, indicated that the percutaneous absorption of azelaic acid occurred only from the most proximal layer of the gel. Furthermore, in both species, the average daily percutaneous flux was two to four times greater with the 20% cream than with the 15% gel, suggesting that the movement of azelaic acid across the skin layer in vivo was enhanced in the cream formulation. The data after a single topical application of cream or gel indicated that, regardless of dose, the percutaneous absorption of azelaic acid was low in both rats and dogs.

TOXICOLOGY

Animal Toxicology

Following single oral doses of azelaic acid administered as a microcrystalline suspension, the minimum lethal doses (MLD) were 3750 mg/kg (male mice) and 5000 mg/kg (female mice and male rats). After intraperitoneal administration, the minimum lethal doses were 400 mg/kg (male rats) and 500 mg/kg (male and female mice). No male rats died after intraperitoneal administration of up to 1000 mg/kg of sodium azelinate. The main clinical signs were apathy, disturbances in gait, prone position (conscious), eyelid closure, distended abdomen (mice, intraperitoneal), ruffled fur (mice and rats, intraperitoneal), accelerated respiration (rats, oral), unconsciousness and tremor (rats, intraperitoneal). Death occurred within 30 minutes to 7 days after intraperitoneal administration and 1.5 to 3 days after oral administration. In dogs, oral doses of 250 mg/kg and higher of azelaic acid, given as capsules, resulted in emesis. The stomach and small intestine were identified as target organs following intraperitoneal administration of high doses of azelaic acid to mice and rats.

No direct compound-related signs of toxicity were observed after repeated oral administration of a microcrystalline suspension of azelaic acid to rats (at a dose level of 1500 mg/kg/day for four weeks or dose levels of 100 and 1000 mg/kg/day for six months) and to monkeys (at a dose level of 250 mg/kg/day for four weeks). In the four-week rat study, the deaths of 15 of 20 rats given 5000 mg/kg (reduced to 3000 mg/kg from Day 3 onwards) were attributed to the amount of substance administered (as evidenced by over-distension of the stomach, obstructive atelectasis of the lungs and/or aspiration pneumonia).

Daily intragastric administration of microcrystalline suspensions of azelaic acid at dose levels up to 2500 mg/kg/day did not affect fertility or reproductive performance in male or female rats or in their untreated offspring. No teratogenicity was observed after oral administration of microcrystalline suspensions of azelaic acid at doses ranging from 50 to 2500 mg/kg/day in inseminated rats, or from 50 to 500 mg/kg/day in pregnant rabbits and pregnant monkeys. Embryolethal effects were noted only after administration of high dosages (2500 mg/kg/day in rats, 150 mg/kg/day in rabbits and 500 mg/kg/day in monkeys). Postnatal development was slightly affected in the offspring of rats orally administered microcrystalline suspensions of azelaic acid at dose levels (500 and 2500 mg/kg/day) which were maternally toxic (increased mortality and decreased body weight). In addition, the viability index was slightly reduced in the F1-generation animals. Development of genitalia, including anogenital distance, was not altered in offspring of rat dams given 2500 mg/kg/day during pregnancy and lactation or during late gestation and lactation.

Embryofetal developmental studies with oral administration of azelaic acid to rats, rabbits, and cynomolgus monkeys during the period of organogenesis revealed embryotoxicity at doses where some maternal toxicity was noted. No teratogenic effects were observed. The embryofetal NOAEL was 32 times the MRHD based on BSA in rats, 6.5 times the MRHD based on BSA in rabbits and 19 times the MRHD based on BSA in monkeys.

In a peri- and post-natal developmental study in rats where azelaic acid was administered orally from gestational day 15 to through day 21 postpartum slight disturbances in the post-natal development of fetuses were noted at oral doses that generated some maternal toxicity. The

NOAEL was 3 times the MRHD based on BSA. No effects on sexual maturation of the fetuses were noted in this study.

Azelaic acid was not a gene mutagen in bacterial cells or in somatic mammalian cells in vitro, in the presence or absence of an extrinsic metabolizing system. Azelaic acid was not clastogenic in human lymphocytes in vitro, in the presence and absence of an extrinsic metabolizing system and was not a mutagen in vivo in the dominant lethal assay or micronucleus assay in mice.

Azelaic acid was not a contact sensitizer in a maximization test conducted in guinea pigs.

The slight irritation observed in dogs was consistent with the results of a study in which the dermal tolerance of 28 daily applications of 250 mg azelaic acid 20% cream to the intact and scarified skin of albino rabbits (5 hrs/day, without occlusion), was compared with the dermal tolerance of 28 daily applications of similar amounts of tretinoin and benzoyl peroxide. Slight incompatibility reactions were observed histologically for the azelaic acid 20% cream and for benzoyl peroxide, while more pronounced incompatibility reactions were observed after repeated application of tretinoin. Similarly, single or repeated applications of azelaic acid 15% gel or the placebo gel formulation to the intact skin of albino rabbits produced slight incompatibility reactions.

Primary, ocular tolerance studies in rabbits revealed moderate to severe ocular irritation with a preservative-free formulation of azelaic acid 20% cream. This irritation was judged to be mainly due to azelaic acid itself because the vehicle alone caused only slight irritation. Administration of a single dose of azelaic acid 20% cream to the monkey eye led to pain reactions immediately after dosing that disappeared after rinsing with water.

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 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 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.

Special Tolerance Studies in Humans

FINACEA was found to have some irritation potential in tests employing exaggerated use (repetitive application under occlusion and/or to damaged skin) in healthy volunteers.

With similar exaggerated use in sensitization protocols, no evidence of a sensitization potential was found in 253 subjects with healthy skin.

No evidence of photosensitization or phototoxicity involving 33 and 12 healthy subjects, respectively, was found. Furthermore, FINACEA does not appear to absorb UV light.

The nature of adverse events and the absence of severe or serious reactions were similar in the different tests. No systemic adverse events were regarded as related to the drug. All drug-related adverse events were cutaneous and mild or moderate in severity. The frequency of related cutaneous adverse events differed in the special tolerance studies in humans, most probably due

to the different application modes (prolonged, repeated occlusive application versus application to damaged skin). Moreover, the frequency and severity reflects the exaggerated use and not the clinically intended use of twice daily application.

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PART III: CONSUMER INFORMATION

PrFINACEA®
azelaic acid gel

This leaflet is Part III of a three-part "Product Monograph" published when FINACEA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FINACEA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

FINACEA is used to treat rosacea (when the skin on the face is unusually red). FINACEA is for topical use only. This means that it is put on the skin.

What it does:

FINACEA is believed to reduce the production of substances known to contribute to inflammation (eg, cathelicidin, killikrein-5) thereby reducing the inflammation of rosacea.

When it should not be used:

Do not use FINACEA if you are allergic or hypersensitive to azelaic acid, propylene glycol or to any of the other ingredients in FINACEA. See the section titled "What the important non medicinal ingredients are" in this leaflet.

What the medicinal ingredient is:

azelaic acid gel, 15% w/w

What the important nonmedicinal ingredients are:

benzoic acid, disodium edetate, lecithin, polyacrylic acid, polysorbate 80, propylene glycol, medium-chain triglycerides, sodium hydroxide

What dosage forms it comes in:

FINACEA is available as gel (15% w/w) in tubes of 5 g and 50 g.^b

WARNINGS AND PRECAUTIONS

BEFORE you use FINACEA, talk to your doctor or pharmacist if:

- you are pregnant, planning to become pregnant, breastfeeding or planning to breastfeed.

^b Not all presentations may be available in Canada.

Children and Adolescents:

The safety and effectiveness of FINACEA in children and adolescents has not yet been established.

INTERACTIONS WITH THIS MEDICATION

There have been no formal studies evaluating the interaction of FINACEA with other drugs.

PROPER USE OF THIS MEDICATION

Usual adult dose:

Before applying FINACEA, the skin should be thoroughly cleaned with water or with a mild skin-cleansing agent. Pat dry with a soft towel before applying FINACEA.

Apply FINACEA sparingly to the affected skin areas twice a day, in the morning and evening, and rub it gently into the skin. About one finger-tip length (i.e. 2.5 cm or 1 inch) of gel squeezed from the tube is sufficient for your entire face. Avoid contact with the eyes, since it might irritate them.

In case of accidental contact of FINACEA with the eyes, inside of the nose, or mouth, wash your eyes, nose or mouth immediately with large quantities of water. If your eyes continue to hurt, tell your doctor.

If your skin becomes irritated, you should either:

- reduce the amount of FINACEA you apply each time; or
- apply it only once a day; or
- stop treatment for a few days.

Always wash your hands after using FINACEA.

Do not cover the treated area with dressings. Avoid alcoholic cleansers, tinctures and astringents, as well as abrasives and peeling agents.

Medication-free cosmetics or cosmetics which do not cause acne may be applied after FINACEA has dried.

Make sure very young children do not touch the treated area of your skin because of the mild irritant effect of FINACEA.

The length of time for which FINACEA must be used varies from person to person and also depends upon the severity of rosacea when you start treatment.

You should see a distinct improvement after about four to eight weeks. FINACEA should be used only as prescribed by your doctor.

If you have rosacea, you should avoid spicy foods, hot foods and drinks, and alcoholic drinks, since these may make

rosacea worse. You should also use only mild skin-cleansing products to wash your face.

FINACEA will not affect your ability to drive and use machines.

Overdose:

FINACEA is for use on the skin only. If you apply too much and your skin becomes irritated, talk with your doctor. You may be instructed to start using less FINACEA less frequently, or to stop using FINACEA altogether until the irritation goes away.

Missed dose:

Do not use increased amounts of FINACEA to make up for a dose that you missed. Continue with your usual dosing schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, FINACEA can have side effects. Skin irritation may occur, usually at the start of treatment. Common undesirable side effects include burning/stinging/tingling or itching sensations, reddening, skin dryness and scaling. Allergic skin reaction and infection of the hair follicle are uncommon side effects. In the majority of cases, the irritation symptoms are mild and go away over the course of treatment.

In very rare cases, allergic skin reactions may occur to azelaic acid or any of the nonmedicinal ingredients.

The following additional side effects have been observed outside of clinical trials:

- Hypersensitivity, which may occur with one or more of the following side effects: rapid swelling under the skin, eye swelling, swelling face, shortness of breath
- Hives

No serious side effects related to the use of FINACEA have been reported.

If you see any unusual changes in your skin colour, you should see your doctor.

If you notice side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking FINACEA, contact your doctor or pharmacist.

HOW TO STORE IT

Store FINACEA at room temperature (15 – 30°C). Keep FINACEA out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or LEO Pharma Medical Information at 1-800-263-4218 or medical-info.ca@leo-pharma.com.

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.leo-pharma.ca> or by contacting the manufacturer at the above-mentioned phone number and e-mail address.

This leaflet was prepared by LEO Pharma Inc.

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