PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ARAZLO™

Tazarotene Lotion
0.045% w/w
Topical

Acne Therapy

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Canada

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ARAZLO™ (tazarotene lotion), is indicated for:

- For the topical treatment of acne vulgaris in patients 10 years of age and older.

1.1 Pediatrics

Pediatrics (≥ 10 years of age)
The safety and efficacy of ARAZLO in pediatric patients (10 years of age and older) has been established. In a clinical pharmacokinetic study, systemic exposure of tazarotene and tazarotenic acid were substantially higher in subjects 10 to <12 years of age than subjects ≥12 years of age due to higher surface area to volume ratio of younger subjects. Therefore, Health Canada recommends that application of ARAZLO in this age group be limited to the face (see 7 WARNINGS AND PRECAUTIONS; 10 ACTION AND CLINICAL PHARMACOLOGY; 14 CLINICAL TRIALS).

Safety and efficacy of ARAZLO in children below the age of 10 years has not been established. Therefore, Health Canada has not authorized an indication in pediatric patients less than 10 years of age.

1.2 Geriatrics

Geriatrics (> 65 years of age)
A limited number of subjects aged > 65 years have been treated with ARAZLO in clinical trials, therefore the safety and efficacy have not been established in this patient population (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

ARAZLO (tazarotene lotion) is contraindicated in the following:

- Patients who are hypersensitive to retinoic compounds or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- In women who are pregnant or may become pregnant ARAZLO may cause fetal harm when administered to a pregnant patient (see 7 WARNINGS AND PRECAUTIONS, Sexual Health, Reproduction; and 7.1.1 Pregnant Women).
- Topical retinoids should not be used in the presence of seborrheic dermatitis.

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

ARAZLO should be applied in a thin layer to the affected area once a day on clean and dry skin.

In pediatric patients 10 to less than 12 years of age, it is recommended that the application be

limited to the face only. Health Canada has not authorized an indication in pediatric subjects less than 10 years of age (see 1 INDICATION; 7 WARNINGS AND PRECAUTIONS).

Concomitant use with oxidizing agents, such as benzoyl peroxide should be avoided. If the concomitant use of ARAZLO with oxidizing agents is required, apply each at different times of the day (e.g. one in the morning and the other in the evening).

4.4 Administration

Apply a thin layer of ARAZLO once daily on affected areas and rub in gently. For face application, dot onto the chin, cheeks, nose, and forehead, then gently rub over the entire face. If a bath or shower is taken prior to application, the skin should be dry before applying the lotion.

Wash hands after applying ARAZLO. If needed, use a moisturizer before or after the use of ARAZLO and allow sufficient time for the skin to dry between both applications.

Avoid the eyes, mouth, paranasal creases, and mucous membranes. If ARAZLO gets in or near eyes, rinse thoroughly with water.

Treatment should be discontinued when control has been achieved. Treatment may be reinitiated as necessary. Intermittent use should be the least number of applications that will prevent recurrence of acne.

4.5 Missed Dose

Apply the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next dose. Do not use extra medicine to make up the missed dose.

5 OVERDOSAGE

If ARAZLO is applied excessively, neither more rapid nor better results will be obtained and marked redness, peeling, or discomfort may occur. In this event, discontinue use and wait until the skin has recovered.

Inadvertent oral ingestion of tazarotene may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis) or other retinoids, including teratogenesis in women of childbearing age. If accidental oral ingestion occurs, the patient should be monitored, and appropriate supportive measures should be administered as necessary, including pregnancy testing in women of childbearing age.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients*
Topical	Lotion Tazarotene (0.045%) Each gram of ARAZLO contains 0.45 mg (0.045%) Tazarotene in a hydrating lotion with Diethyl Sebacate, Light Mineral Oil, Sorbitol Solution 70%	Carbomer Copolymer Type B, Carbomer Homopolymer Type A, Diethyl Sebacate, Edetate Disodium Dihydrate, Light Mineral Oil, Methylparaben, Propylparaben, Purified Water, Sodium Hydroxide, Sorbitan Monooleate and Sorbitol Solution 70%.

*Does not include any fragrance, colorant or alcohol

ARAZLO is a white to off-white, lightweight, non-greasy lotion supplied in a 45 g white aluminum tube. Physicians' samples are supplied in 3 g white aluminum tubes. It is provided in a formulation with known hydrating and moisturizers such as diethyl sebacate, light mineral oil and sorbitol solution which may alleviate dryness of skin.

7 WARNINGS AND PRECAUTIONS

General

ARAZLO is for external topical use only. Not for oral, ophthalmic, or intravaginal use.

Avoid contact with the eyes, eyelids, angles of the nose, lips, mucous membranes, severely inflamed skin or to open lesions or to other areas where treatment is not intended. In the event of contact with the eye, flush with cold water.

ARAZLO is not recommended for use on the scalp, axillae, or intertriginous areas.

Sexual Health

Reproduction
ARAZLO is contraindicated in women who are pregnant or may become pregnant (see 2 CONTRAINDICATIONS; 7.1.1 Pregnant Women).

Skin

Use of topical tazarotene may produce contact dermatitis. If burning/stinging, itching, and dryness become more severe, the medication should either be discontinued until the integrity of the skin is restored or the dosing should be reduced to an interval the patient can tolerate. Discontinue and do not resume treatment if allergic contact dermatitis is identified.
Patients using ARAZLO may experience application site pain, dryness, exfoliation, erythema,

and pruritus. Depending upon severity of these signs and symptoms, instruct patients to use a moisturizer, reduce the frequency of the application of ARAZLO, or discontinue use. Therapy can be resumed, or the frequency of application can be increased, as the patient becomes able to tolerate treatment.

Avoid use of concomitant medications and cosmetics that have a strong drying effect. It is recommended to postpone treatment with ARAZLO until the drying effects of these products subside.

Avoid application of ARAZLO to eczematous or sunburned skin.

Use effective sunscreens and wear protective clothing while using ARAZLO. Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO.

Photosensitivity and Risk for Sunburn
Topical administration of tazarotene has been shown to be associated with increased phototoxicity. As tazarotene is a component of ARAZLO, exposure to sunlight (including sunlamps) should be avoided during the use of ARAZLO. Patients should be instructed to use sunscreens (minimum SPF of 15) and protective clothing on areas treated with ARAZLO. Patients with sunburn should be advised not to use ARAZLO on the sunburnt areas until fully recovered.

Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution.

ARAZLO should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

7.1 Special Populations

7.1.1 Pregnant Women

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient. Since the potential risk to the fetus outweighs the potential benefit to the mother, ARAZLO is contraindicated in women who are pregnant or may become pregnant (see 2 CONTRAINDICATIONS).

There have been rare reports of birth defects among babies born to women exposed to topical retinoids during pregnancy. However, there are no adequate and well-controlled prospective studies on the use of tazarotene or other topical retinoids during pregnancy to inform any drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, the safety and efficacy of tazarotene 0.045% lotion in pregnant women has not been established.

Women of childbearing potential should be warned of the potential risk and use adequate birth-control measures when ARAZLO is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. Confirmation that the patient is not pregnant should be received prior to starting treatment and before each new treatment course. ARAZLO therapy should begin during a menstrual period.

In animal reproduction and developmental studies, tazarotene produced teratogenic and developmental effects commonly associated with retinoids after topical or systemic administration in rats and rabbits (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. In patients treated topically over sufficient body surface area, exposure could be in the same order of magnitude associated with teratogenicity in orally treated animals. Tazarotene, like other retinoids, is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans.

If ARAZLO is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

7.1.2 Breast-feeding

The safe use of ARAZLO during breast-feeding has not been established.

It is not known whether tazarotene or its metabolites are excreted in human milk following the topical application of ARAZLO; however, tazarotene has been detected in the milk of lactating rats exposed to 14C-tazarotene gel formulation. A decision to discontinue breastfeeding or discontinue the drug should be based on the mother's clinical need for ARAZLO taking into account any potential adverse effects on the breastfed child from ARAZLO and developmental and health benefits of breastfeeding.

Because some tazarotene may be excreted in human milk, caution should be exercised when ARAZLO is used by a nursing woman.

Breastfeeding women should not apply ARAZLO directly to the nipple and areola to avoid direct infant exposure.

7.1.3 Pediatrics

Pediatrics
Safety and efficacy of ARAZLO for the topical treatment of acne vulgaris was assessed in 344 pediatric patients aged 10 years and older in two 12-week pivotal Phase 3 clinical trials. However, only a limited number of patients (n=14) received ARAZLO in the preadolescent age group of 10 to < 12 years of age and systemic exposures of tazarotene and tazarotenic acid were substantially higher in subjects 10 to <12 years of age than subjects ≥12 years of age. Therefore, Health Canada recommends that application of ARAZLO in this age group be limited to face (see 1 INDICATIONS; 14 CLINICAL TRIALS).

Safety and effectiveness of ARAZLO in children below the age of 10 years have not been established. Therefore, Health Canada has not authorized an indication in pediatric patients less than 10 years of age.

7.1.4 Geriatrics

A limited number of subjects aged > 65 years have been treated with ARAZLO in clinical trials,

therefore the safety and efficacy have not been established in this patient population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Across the clinical studies that contributed to the evaluation of safety for ARAZLO, the most frequently reported events were generally associated with application site reactions and other related, topical skin events. Most events were mild or moderate in severity. Few events across studies were serious and none of the serious adverse events (SAEs) were considered by the investigator to be treatment related.

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In 2 multicenter, randomized, double-blind, vehicle-controlled clinical trials, subjects age 9 years and older applied ARAZLO or vehicle once daily for 12 weeks. The majority of subjects were white (74%) and female (66%). Out of a total of 779 subjects who applied ARAZLO: 42% of subjects were younger than 18 years of age and 1.8% were between 9 years to less than 12 years of age. Adverse reactions reported by ≥1% of subjects treated with ARAZLO and more frequently than subjects treated with vehicle are summarized in **Table 2.** Most adverse reactions were mild to moderate in severity. Severe adverse reactions represented 1.3% of the subjects treated with ARAZLO. Overall, 2.8% (22/779) of subjects discontinued ARAZLO because of TEAEs.

Table 2: Pooled Pivotal Phase 3 Studies (V01-123A-301 and V01-123A-302): Treatment Emergent Adverse Events Experienced by ≥ 1% of the Subjects in Either Treatment Group by System Organ Class and Preferred Term

System Organ Class[a] Preferred Term	ARAZLO (N=779)	Vehicle Lotion (N=791)
General Disorders and Administration Site Conditions		
Application Site Pain	41 (5.3)	2 (0.3)
Application Site Dryness	30 (3.9)	1 (0.1)
Application Site Exfoliation	16 (2.1)	0 (0.0)
Application Site Erythema	15 (1.9)	0 (0.0)
Application Site Pruritus	10 (1.3)	0 (0.0)
Infections and Infestations		
Viral Upper Respiratory Tract Infection	36 (4.6)	31 (3.9)
Upper Respiratory Tract Infection	13 (1.7)	14 (1.8)

System Organ Class[a] Preferred Term	ARAZLO (N=779)	Vehicle Lotion (N=791)

TEAE = treatment-emergent adverse event
[a] Counts reflect numbers of subjects reporting one or more adverse events that map to MedDRA. At each level of summarization (System Organ Class or Preferred Term) subjects are counted once.

Counts reflect numbers of subjects reporting 1 or more TEAEs that map to system organ classes or preferred terms. At each level of summarization (system organ class or preferred term), subjects are counted once.

System organ classes are included only if at least 1 preferred term within that class was experienced by ≥ 1% of the subjects in either treatment group.

Most individual Treatment Emergent Adverse Events (TEAE) reported in both studies (V01-123A-301 and V01-123A-302) were experienced by 1 or 2 subjects each. Of the events that occurred in ≥ 1% of the subjects for ARAZLO, almost all were associated with application site reactions; none of these reactions were unexpected for tazarotene or for a topical, facial, acne treatment. It was observed that the application site reactions predominantly occurred for the patients using ARAZLO, while other events generally occurred at similar frequencies in both treatment groups.

The events occurring at the 3 highest frequencies for ARAZLO were application site pain (5.3%), viral upper respiratory tract infection (4.6%), and application site dryness (3.9%).

8.3 Less Common Clinical Trial Adverse Reactions (< 1% and More Frequent than the Vehicle in Pooled Pivotal Phase 3 Studies [V01-123A-301 and V01-123A-302])

Blood and lymphatic system disorders: Eosinophilia

General disorders and administration site conditions: Pain, administration site pain, application site dermatitis, application site erosion.

Gastrointestinal disorders: Diarrhoea

Immune system disorders: Hypersensitivity

Infections and infestations: Gastroenteritis, bacterial vaginosis

Injury, poisoning and procedural complications: Arthropod bite

Musculoskeletal and connective tissue disorders: Back pain, arthralgia

Skin and subcutaneous tissue disorders: Eczema, rash, erythema

Respiratory, thoracic and mediastinal disorders: Nasal congestion

Reproductive system and breast disorders: Dysmenorrhoea

Cutaneous Safety and Tolerability Assessments

Cutaneous safety and tolerability at the drug application site were evaluated through active assessments of scaling, erythema, hypopigmentation, hyper-pigmentation, itching, burning, and stinging, with grades for none, mild, moderate, and severe. Overall, the incidence and mean scores of erythema, scaling, burning, stinging and itching was higher in the ARAZLO group as compared to the vehicle group at any post-baseline visit; however, the signs and symptoms were generally mild-to-moderate in severity. Subjects treated with ARAZLO showed transient increases in severity that peaked around Week 2 for most parameters and improved over the course of the study. At Week 12, most subjects showed small changes relative to baseline in nearly all assessed parameters.

Table 3: Pooled Pivotal Phase 3 Studies (V01-123A-301 and V01-123A-302): Incidence of Cutaneous Safety and Tolerability parameters by Severity and Study Visits.

	Baseline (Prior to Treatment)				Maximum Postbaseline				Week 12 (End of Treatment)			
	None	Mild	Mod	Severe	None	Mild	Mod	Severe	None	Mild	Mod	Severe
ARAZLO Lotion (N=779)												
Scaling, %	90.9	9.0	0.1	0.0	49.1	40.4	10.2	0.3	84.4	14.0	1.4	0.1
Erythema, %	73.4	19.1	7.1	0.4	51.1	36.6	11.9	0.4	76.4	20.6	2.9	0.1
Hypo-pigmen-tation, %	96.7	3.1	0.3	0.0	95.9	3.6	0.5	0.0	97.8	2.0	0.1	0.0
Hyper-pigmen-tation, %	81.4	13.9	4.6	0.1	74.6	18.6	6.7	0.1	85.4	12.4	2.2	0.1
Itching, %	90.4	8.3	1.2	0.1	70.7	22.5	6.6	0.3	92.8	6.1	1.2	0.0
Burning, %	98.2	1.3	0.5	0.0	69.4	20.4	8.9	1.3	95.0	3.7	1.0	0.3
Stinging, %	98.3	1.7	0.0	0.0	77.4	16.5	5.5	0.5	95.1	4.2	0.6	0.1
ARAZLO Vehicle Lotion (N = 791)												
Scaling, %	91.7	8.0	0.3	0.1	77.2	21.5	1.3	0.0	92.3	7.3	0.4	0.0
Erythema, %	72.8	21.5	5.4	0.3	62.0	31.5	6.2	0.3	81.7	16.3	1.9	0.0
Hypo-pigmen-tation, %	96.0	3.5	0.5	0.0	95.7	4.2	0.1	0.0	97.6	2.2	0.1	0.0
Hyper-pigmen-tation, %	81.4	15.2	4.0	0.4	76.1	17.0	6.5	0.5	83.3	12.7	3.6	0.4
Itching, %	90.5	7.8	1.6	0.0	86.3	11.3	2.2	0.3	96.3	2.9	0.8	0.0
Burning, %	97.6	1.9	0.4	0.1	94.2	5.3	0.4	0.1	98.3	1.7	0.0	0.0
Stinging, %	97.9	1.9	0.3	0.0	95.2	4.3	0.5	0.0	98.3	1.1	0.1	0.0

Mod = moderate

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

There were no findings related to hematology or chemistry treatment-related in any of the studies that included subjects with acne vulgaris in patients 10 years of age and older.

9 DRUG INTERACTIONS

9.1 Drug interactions overview

No formal drug-drug interaction studies were conducted with ARAZLO.

The systemic absorption of tazarotene and tazarotenic acid from ARAZLO is minimal as demonstrated in the results from the maximum use pharmacokinetic study (see 10.3 Pharmacokinetics).

Concomitant dermatologic medications and cosmetics that have a strong drying effect or high amounts of alcohol, astringents, spices, lime peel, medicated soaps or shampoos, permanent wave solution, or other products that may irritate the skin should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of ARAZLO begins.

ARAZLO should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Concomitant use with oxidizing agents, as benzoyl peroxide, may cause degradation of tazarotene and may reduce the clinical efficacy of tazarotene.

The impact of tazarotene on the pharmacokinetics of progestin only oral contraceptives (i.e., mini pills) has not been evaluated.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tazarotene is a retinoid prodrug which is converted to its active form, tazarotenic acid, the carboxylic acid of tazarotene, by deesterification. Tazarotenic acid may modify gene expression and binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ and RARγ, but shows relative selectivity for RARβ, and RARγ, the receptor subtype present in keratinocytes and recognized to be the most relevant in acne. The mechanism of tazarotene action in acne is unknown.

Acne is a multifactorial disease. The four main factors involved in its development are excessive follicular keratinization, hyperactivity of the sebaceous gland, proliferation of *Cutibacterium acnes (C. Acnes)* and other microbes found in sebum-rich skin, and perifollicular inflammation.

The basis of tazarotene's therapeutic effect in acne vulgaris appears to be due to its anti-hyperproliferative, normalizing-of-differentiation and anti-inflammatory effects.

10.3 Pharmacokinetics

Following application, the drug undergoes esterase hydrolysis to its primary active metabolite, “tazarotenic acid” (the only metabolite of tazarotene known to have retinoid activity), and oxidative metabolism to inactive sulfoxide and sulfone derivatives. Little parent compound can be detected in the plasma. “Tazarotenic acid” is highly bound to plasma proteins (>99%). The half-life of “tazarotenic acid” following topical application of tazarotene gel is similar in normal and psoriatic subjects, approximately 18 hours.

Systemic exposure following topical application of ARAZLO was evaluated in 28 subjects in an open label, randomized, pharmacokinetic study. Subjects aged 9 years and older with moderate to severe acne applied approximately 4 grams of ARAZLO to the entire face (excluding eyes and lips), neck, upper chest, upper back and shoulders once daily for 14 Days.

The majority of collected samples had concentrations below the limit of quantification (LOQ) for tazarotene (0.005 ng/mL). For subjects 12 years and older, the mean C_{max} and mean $AUC_{(0-t)}$ values for tazarotene from quantifiable samples were 3.22 pg/mL and 67.40 h*pg/mL respectively, on Day 14 to 15. For subjects 9 to <12 years, the mean C_{max} and mean $AUC_{(0-t)}$ values for tazarotene from quantifiable samples were 17.82 pg/mL and 240.98 h*pg/mL, respectively, on Day 14 to 15. Therefore, the mean C_{max} and $AUC_{(0-t)}$ of tazarotene in subjects aged 9 to less than 12 years was approximately 3.7 and 3.6-fold higher, respectively, compared to that observed in subjects 12 years and older.

Tazarotenic acid concentrations were measurable in the majority of samples following single and repeated topical administration of ARAZLO (LOQ = 0.005 ng/mL). For subjects 12 years and older, the mean C_{max} and $AUC_{(0-t)}$ values for tazarotenic acid from quantifiable samples were 262.63 pg/mL and 4129.33 h*pg/mL, respectively, on Days 14 to 15. For subjects 9 to <12 years, the mean C_{max} and mean $AUC_{(0-t)}$ values for tazarotenic acid from quantifiable samples were 620.88 pg/mL and 9702.49 h*pg/mL, respectively, on Day 14 to 15. Therefore, the mean C_{max} and $AUC_{(0-t)}$ of tazarotenic acid in subjects aged 9 to less than 12 years was approximately 2.4 and 2.3-fold higher, respectively, compared to that observed in subjects 12 years and older.

11 STORAGE, STABILITY AND DISPOSAL

Keep out of reach and sight of children.

ARAZLO should be stored at room temperature (15-30°C).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

ARAZLO contains tazarotene as the active ingredient in a white to off-white, lightweight, non-greasy lotion formulation intended for topical use. The ARAZLO formulation uses a polymeric emulsification system (PRISMATREX™) which maintains the emulsion droplets size distribution stable across time and temperature. This system provides stable emulsions by anchoring its hydrophobic portions and forming an adsorbed gel layer around each oil droplet. The product's target pH (5.0 – 6.0) is controlled by the amount of polymer and base (sodium hydroxide) present in the formulation. This pH range is consistent with the pH tolerated by the skin without inducing irritation.

Drug Substance

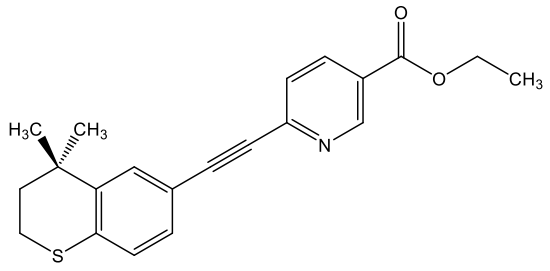
Common name: Tazarotene

Chemical name: 6-[2-(3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl) ethynyl]-3-pyridinecarboxylic acid, ethyl ester.

Molecular formula: $C_{21}H_{21}NO_2S$

Molecular mass: 351.46 g/mol

Structural formula:



Physicochemical properties

Description: Pale yellow to brownish powder

Melting Point: Melting point of 104ºC

Solubility: Practically insoluble and is soluble in non-aqueous solvents.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics (Pivotal Studies)

The clinical development program for ARAZLO consisted of 2 identical, prospective, randomized, multicenter, double-blind parallel-group, vehicle-controlled, pivotal Phase 3 safety and efficacy studies (V01-123A-301 and V01-123A-302). These studies assessed the safety, tolerability, and clinical efficacy of once daily use of ARAZLO relative to its vehicle for the topical treatment of moderate to severe facial acne vulgaris in patients 9 years of age and older.

Table 4 - Summary of patient demographics for clinical trials for topical treatment of acne vulgaris

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
V01-123A-301 Efficacy (Pivotal)	Phase 3, Multicenter, Parallel-Group, Randomized, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of ARAZLO in the treatment of moderate to severe acne	Once daily topical application of randomized study drug for 12 weeks	813 subjects were randomized • 402 to ARAZLO • 411 to Vehicle Lotion	Mean age: 20.6 years (9-65 years)	262 Male (32.2.0%) 551 Female (67.8%)
V01-123A-302 Efficacy (Pivotal)	Phase 3, Multicenter, Parallel-Group, Randomized, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of ARAZLO in the treatment of moderate to severe acne	Once daily topical application of randomized study drug for 12 weeks	801 subjects were randomized • 397 to ARAZLO • 404 to Vehicle Lotion	Mean age: 20.3 years (9-54 years)	288 Male (36%) 513 Female (64%)

Enrollment Criteria
Enrolled subjects in the clinical development program had a score of moderate (3) or severe (4) on the Evaluator's Global Severity Score (EGSS), 20 to 50 inflammatory lesions (papules, pustules, and nodules), 25 to 100 noninflammatory lesions (open and closed comedones), and 2 or fewer facial use **(see Table 5)**.

Table 5 – Evaluator's Global Severity Score (EGSS)

0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost Clear	Rare noninflammatory lesions and papules
2	Mild	Some noninflammatory lesions are present and a few inflammatory lesions
3	Moderate	Noninflammatory lesions predominate; Many comedones and papules/pustules. There may be 1 nodulocystic lesion.
4	Severe	Inflammatory lesions are more apparent. Many comedones and papules/pustules. There may be up to 2 nodulocystic lesions

Subject Demographics
A total of 1614 subjects were randomized, including 799 in the ARAZLO Lotion and 815 in the Vehicle Lotion group. In the intention-to-treat (ITT) analysis set, the subjects had a mean age of 20.5 years (range = 9 to 65 years). Most of the subjects were female (66%), and white (74%). Approximately, 42% of subjects were younger than 18 years of age and 1.8% were between 9 years to less than 12 years of age.

Efficacy Evaluation
The coprimary efficacy endpoints of treatment success on the EGSS, absolute change in noninflammatory lesion count, and absolute change in inflammatory lesion count were assessed at Week 12. Treatment success on the EGSS was defined as at least a 2-grade improvement from Baseline and an EGSS score of clear (0) or almost clear (1). In order to draw a conclusion of superiority regarding ARAZLO Lotion relative to its vehicle, the analyses of all 3 coprimary efficacy endpoints must have yielded significant results at an alpha level of 0.05. A difference of ≥10% compared to vehicle in all three coprimary efficacy endpoints was defined as being clinically meaningful.

The efficacy analysis of ARAZLO Lotion relative to its vehicle also included several secondary and supportive efficacy endpoints (see section 12.2 Study Results).

14.2 Study Results

In two large vehicle-controlled clinical trial studies, ARAZLO applied once daily was significantly more effective than vehicle in achieving treatment success, and in reducing mean absolute reduction in inflammatory and noninflammatory lesion counts. The efficacy results are presented in **Table 6**.

Table 6 –Efficacy Results at Week 12

	Trial 301		Treatment Difference (95% Confidence Interval)	Trial 302		Treatment Difference (95% Confidence Interval)
	ARAZLO	Vehicle		ARAZLO	Vehicle	
	N=402	N=411		N=397	N=404	
EGSS						
Treatment Success[a]*	25.5%	13%	12.5% (7.1%, 17.9%)	29.6%	7.3%	12.3% (6.5%, 18.1%)
Non-Inflammatory Lesions						
Mean Absolute Reduction[a]	21.0	16.4	4.6 (2.6, 6.4)	24.6	16.6	8.0 (5.9, 10.2)
Mean Percent Reduction†	51.4%	41.5%	-	60%	41.6%	-
Inflammatory Lesions						
Mean Absolute Reduction[a]	15.6	12.4	3.2 (1.9, 4.7)	16.7	13.4	3.3 (1.9, 4.5)
Mean Percent Reduction†	55.5%	45.7%	-	59.5%	49%	-

* Treatment success on the defined as percentage of patients with at least a 2-grade reduction from baseline and an EGSS score of clear (0) or almost clear (1) at Week 12

† secondary endpoint

[a] $p < 0.001$ for each pairwise comparison in both studies

All co-primary endpoints (absolute change from baseline in inflammatory and noninflammatory lesion counts and Treatment Success) showed significantly superior results for ARAZLO compared to Vehicle group at Week 12.

Both pivotal Phase 3 studies yielded similar results across their coprimary efficacy endpoints demonstrating consistency regarding the efficacy of ARAZLO in the treatment of acne when applied once daily for 12 weeks.

Overall, the results of the secondary and supportive efficacy endpoint analysis in two studies (301 and 302) and integrated data from these studies supported the results of the coprimary efficacy endpoints. Both studies met 6 out of 7 secondary efficacy endpoints, i.e., the differences between the two groups were significant for percentage change in noninflammatory lesion count at Weeks 12, Week 8 and Week 4, percent change in inflammatory lesion counts at weeks 12 and 8, and proportion of subjects with at least a 2-grade reduction from Baseline in EGSS at Week 12. The difference between treatment groups at Week 4 in inflammatory lesion counts, however, was not significant. The changes from baseline for two supportive efficacy endpoints (i.e. percent change in noninflammatory lesion counts from Baseline to Week 2 and at least 2 Grade reductions in EGSS from Baseline to Week 8) showed numerically higher values ARAZLO Lotion as compared to the Vehicle Lotion. These results, however, were considered nominal since the gated significance testing stopped at the final step for secondary efficacy endpoints.

Subgroup analysis
In both Phase 3 studies and in the integrated analysis, there were no meaningful differences in treatment effect for any coprimary efficacy endpoint according to age (median age of <19 vs. ≥19 years of age), sex, race, ethnicity, and baseline EGSS (i.e., disease severity). Furthermore, the treatment effects for all coprimary efficacy endpoints were generally larger in the ARAZLO Lotion group than in the Vehicle Lotion group for all evaluated subgroups where the sample size was sufficient to make comparisons. Note that the trials were not powered to detect differences in subgroups; therefore, the results should be interpreted with caution.

Additional statistical analyses were conducted for the following subgroups of age i.e., 9 to <12 years, 12 to <18 years of age, <18 years of age, and ≥ 18 years of age. In both Phase 3 studies, and in the integrated analysis, the differences between the ARAZLO Lotion and the Vehicle Lotion group at Week 12 were statistically significant for all three co-primary efficacy endpoints in subjects aged 12 years and above. For the subgroup of 9 to <12 years of age, numerically greater effect was noted for ARAZLO Lotion as compared to the Vehicle Lotion for all three coprimary efficacy endpoints in the integrated analysis. The results, were, however, not statistically significant, likely due to the small number of subjects enrolled in this age group (n=14 in the ARAZLO Lotion group in the integrated analysis). Since the pathophysiology and disease course of acne vulgaris is similar across these pediatric age groups, the drug's mechanism of action is also likely to be comparable across these pediatric age groups. Therefore, it is expected that the response to ARAZLO in the subgroup of 9 to <12 years of age would be similar to the pediatric age cohort of 12 to <18 years.

15 MICROBIOLOGY

ARAZLO is not an antimicrobial drug.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity
A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to the Maximum Recommended Human Dose (MRHD) (based on AUC comparison).

A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals. Tazarotenic acid systemic exposures at the highest dose was 7 times the MRHD (based on AUC comparison).

Tazarotene gel (0%, 0.001%, 0.005% and 0.01%) produced photocarcinogenicity in a 40-week study in which tazarotene was administered topically to hairless mice along with ultraviolet radiation (UVR) exposure once daily for 5 days a week. Similar enhancement of photocarcinogenesis has been demonstrated for related compounds, including the topical retinoid tretinoin, at concentrations of 0.001% and 0.01% .

Mutagenesis
Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in an in vivo mouse micronucleus test.

Tazarotene was not mutagenic in the Ames and CHO/HGPRT mammalian cell forward gene mutation assays and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was not clastogenic in an in vivo mouse micronucleus test.

Reproductive and Developmental Toxicology
Animal fertility studies have not been performed with ARAZLO.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of a tazarotene gel formulation up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat at the highest dose was equivalent to the MRHD (based on AUC comparison).

No impairment of mating performance was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison).

No impairment of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages , decrease number of implantation sites, decreased litter size, decreased number of live fetuses, decreased fetal body weight, and an increase in developmental effects at that dose which produced a systemic exposure 6 times the MRHD (based on AUC comparison).

In rat and monkey toxicity studies, repeat dermal tazarotene administration was associated with reduced fetal weights and non-reversible bone abnormalities. Oral administration of tazarotene to rats and monkeys was also associated with malformations, including spina bifida, hydroencephaly and heart anomalies (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

17 SUPPORTING PRODUCT MONOGRAPHS

1. TAZORAC® (Tazarotene Cream 0.05% and 0.1% w/w) Product Monograph, Control No.: 187510, Allergan Inc. December 8, 2015.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrARAZLO™
Tazarotene Lotion, 0.045% w/w

Read this carefully before you start taking **ARAZLO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ARAZLO**.

What is ARAZLO used for?

- ARAZLO is used on the skin to treat people 10 years of age and older with acne vulgaris (acne). It is recommended that for children (10 to less than 12 years of age), ARAZLO should be used on the face only.

- Acne vulgaris is a skin condition that begins with the formation of a plug in the hair follicles. The plug is made up of surface skin, oil and bacteria. It is seen as a whitehead or blackhead (comedones). After the formation of the plug, oil in the gland escapes into the surrounding skin and causes inflammation which is seen as papules, pustules, or cysts.

How does ARAZLO work?

- ARAZLO works by helping the normal growth of the skin cells (keratinocytes) and reducing skin inflammation in acne. It is not known exactly how ARAZLO works.
- Your acne should improve as you continue to use ARAZLO.

What are the ingredients in ARAZLO?
Medicinal ingredients: Tazarotene.

Non-medicinal ingredients: Carbomer Copolymer Type B, Carbomer Homopolymer Type A, Diethyl Sebacate, Edetate Disodium Dihydrate, Light Mineral Oil, Methylparaben, Propylparaben, Purified Water, Sodium Hydroxide, Sorbitan Monooleate and Sorbitol Solution 70%.

ARAZLO does not include any fragrance, colorant or alcohol.

ARAZLO comes in the following dosage forms:

- Tazarotene lotion 0.045% w/w.
- It is available in a 45 g tube and 3 g tube samples.

Do not use ARAZLO if:

- you are allergic to other retinoic compounds, or any ingredient found in ARAZLO (see “What are the ingredients in ARAZLO”).
- you are pregnant or if you think you might be pregnant, or plan to become pregnant. ARAZLO may harm your unborn baby. (See “Other warnings you should know about”).
- you have a skin condition known as seborrheic dermatitis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ARAZLO. Talk about any health conditions or problems you may have, including if you:

- have eczema or any other skin problems (such as skin irritation or sunburnt skin).

Other warnings you should know about:

Skin care

- ARAZLO can increase your chances of having sunburns. If you are going to be exposed to sunlight, you should use sunscreen with a minimum SPF of 15 and wear clothes that can protect you from the sun. This includes sunlamps. If you already have a sunburn, wait until it has healed before using ARAZLO. Tell your doctor if you spend a lot of time in the sun, or if you sunburn easily.
- Avoid skin products (such as benzoyl peroxide) or cosmetics, including moisturizers, creams, lotions, or products that can dry out your skin.

Pregnancy and breastfeeding

- If you are pregnant or if you think you might be pregnant, or plan to become pregnant, talk to your healthcare professional. ARAZLO may harm your unborn baby.
    - If you are a woman who is able to get pregnant, you should use an appropriate birth control method while you are using ARAZLO.
    - You should also start using ARAZLO when your period is normal to make sure you are not pregnant.
    - Before you start using ARAZLO, you should confirm with your doctor that you are not pregnant. Your doctor may request a pregnancy test in the 2-week period before ARAZLO treatment.
    - STOP using ARAZLO and tell your healthcare professional right away if you become pregnant.
- Tell your doctor if you are breastfeeding. You and your doctor should decide if the benefits of breastfeeding outweigh any possible harm to the baby. It is not known if it is safe to use ARAZLO and breastfeed. If you breastfeed, do not apply ARAZLO to your nipples or areola (dark part around the nipple). This will help decrease direct exposure of the baby to ARAZLO.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ARAZLO:

- Drugs that make your skin more sensitive to the sun such as thiazides (diuretics), antibiotics (tetracyclines, fluoroquinolones, phenothiazines or sulfonamides).
- Drugs that are applied to the skin or cosmetics that have a strong drying effect. This includes products with high amounts of alcohol, astringents, spices, lime peel, medicated soaps or shampoos, and permanent wave solution.
- Products containing benzoyl peroxide.

How to take ARAZLO:

- Use ARAZLO exactly as your doctor tells you to use it.
- ARAZLO is for skin use only. Do not use ARAZLO in your eyes, nose, mouth or other mucous membranes. If you get ARAZLO in your eye, flush it with cold water.

- Do no use ARAZLO on your scalp, armpits, or areas where two parts of your skin touch (skin folds, thighs, and groin). Do not use ARAZLO on normal skin that does not have acne.
- If you use other medicines on your skin such as benzoyl peroxide during treatment with ARAZLO, you should apply one in the morning and one in the evening to separate the application time.
- You may use a moisturizer after applying ARAZLO as needed. Make sure to allow skin to dry after you apply ARAZLO.

Usual dose:

Adults and children over 10 years of age
Apply a thin layer of ARAZLO to cover the affected areas once a day on clean and dry skin. For face application, dot onto the chin, cheeks, nose, and forehead, then gently rub over the entire face. It is recommended that for children (10 to less than 12 years of age), ARAZLO should be used on the face only.

Wash your hands after applying ARAZLO.

Do not use more than you need to cover the treated areas. Using too much ARAZLO may increase the risk of skin irritation.

If you develop skin irritations, your healthcare provider may tell you to:
- use a moisturizer;
- decrease the number of times you apply ARAZLO;
- completely stop treatment with ARAZLO.

Wind or cold weather may be more irritating to your skin during treatment with ARAZLO.

Overdose:

If you think you, or a person you are caring for, have taken too much ARAZLO, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
Apply the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next dose. Do not use extra medicine to make up the missed dose.

What are possible side effects from using ARAZLO?
These are not all the possible side effects you may feel when taking ARAZLO. If you experience any side effects not listed here, contact your healthcare professional.

Side effects which may occur when using ARAZLO are primarily local effects on the skin. Side effects may happen when your skin is adapting to how ARAZLO works.

Side effects may include:

- Application site pain
- Dryness
- Peeling
- Redness
- Itching
- Sensitivity to sunlight
- Risk of sunburn
- Back and joint pain
- Painful menstrual periods (Dysmenorrhea)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Skin Irritation at the application site: red, sore or peeling skin; burning/stinging sensation; severe itching and/or dryness	√		
Infections and infestations: Viral and upper respiratory tract infection (symptoms include headache, cough, sore throat, runny nose, nasal congestion, fever)		√	
COMMON			
Hypersensitivity (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes			√
UNCOMMON			
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing		√	
Gastroenteritis (inflammation of the stomach and intestines): abdominal pain, diarrhea, nausea, vomiting		√	
Bacterial vaginosis (too much bacteria in the vagina): pain, itching, burning in the vagina, vaginal discharge		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting 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.

Storage:
Store at room temperature (15-30°C).
Keep out of reach and sight of children.

If you want more information about ARAZLO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); by contacting the sponsor: Bausch Health, Canada Inc., 2150 St-Elzéar Blvd. West, Laval, (Quebec) H7L 4A8; or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

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