TAZAROTENE CREAM- tazarotene cream
E. Fougera & Co. a division of Fougera Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAZAROTENE CREAM safely and effectively. See full prescribing information for TAZAROTENE CREAM.

TAZAROTENE cream, for topical use

Initial U.S. Approval: 1997

INDICATIONS AND USAGE

Tazarotene cream, 0.1% is a retinoid indicated as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs. (1)

Limitations of Use:

- Does not eliminate or prevent wrinkles or restore more youthful skin. (1)
- Does not repair sun damaged skin or reverse photoaging. (1)
- Safety and effectiveness for the prevention or treatment of actinic keratoses, skin neoplasms, or lentigo maligna have not been established. (1, 5.4)

DOSAGE AND ADMINISTRATION

- Apply a pea-sized amount of tazarotene cream to lightly cover the entire face once daily at bedtime. (2)
- If contact with eyes occurs, rinse thoroughly with water. (2)
- Not for ophthalmic, oral, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Cream, 0.1%. (3)

CONTRAINDICATIONS

- Pregnancy. (4, 8.1)
- Known Hypersensitivity. (4)

WARNINGS AND PRECAUTIONS

- *Embryo-Fetal Toxicity*: May cause fetal harm when administered to a pregnant woman. Obtain a pregnancy test in females of reproductive potential within 2 weeks prior to initiating treatment. Advise females of reproductive potential to use effective contraception. (5.1)
- *Local Irritation*: Some individuals may experience excessive pruritus, burning, skin redness, or peeling. If these adverse reactions occur, discontinue tazarotene cream until the integrity of the skin has been restored or reduce dosing interval. Avoid using tazarotene cream on eczematous skin, as such use may cause severe irritation. (5.2)
- *Photosensitivity and Risk of Sunburn*: Avoid exposure to sunlight, sunlamps, and weather extremes. Wear sunscreen daily. Avoid using tazarotene cream if the patient is also taking drugs known to be photosensitizers. (5.3)
- *Lentigo Maligna*: Carefully assess facial pigmented lesions of concern before application of tazarotene cream. (5.4)

ADVERSE REACTIONS

Most common adverse events (occurring in ≥10% of patients) are desquamation, erythema, burning sensation, dry skin, skin irritation, and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fougera Pharmaceuticals Inc. at 1-800-645-9833 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tazarotene cream, 0.1% is indicated as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs.

Limitations of Use:

- Tazarotene cream does not eliminate or prevent wrinkles or restore more youthful skin.
- Tazarotene cream does not reverse photoaging or repair sun damaged skin; tazarotene cream does not mitigate coarse or deep wrinkling, tactile roughness, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.
- The safety and the effectiveness of tazarotene cream for the prevention or treatment of actinic keratoses, skin neoplasms, or lentigo maligna have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Assessment Prior to Treatment Initiation

Obtain a pregnancy test within 2 weeks prior to tazarotene cream therapy. Initiate tazarotene cream therapy during a menstrual period *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)]*.

Carefully assess facial pigmented lesions of concern by a qualified physician (e.g., dermatologist) before application of tazarotene cream *[see Warnings and Precautions (5.4)]*.

2.2 Important Administration Instructions

Avoid accidental transfer of tazarotene cream into eyes, mouth, or other mucous membranes. If contact with mucous membranes occurs, rinse thoroughly with water *[see Warnings and Precaution (5.2)]*.

Wash hands thoroughly after application.

Emollients or moisturizers can be applied either before or after applying tazarotene cream. However, ensure that the first cream or lotion has absorbed into the skin and has dried completely before subsequent cream or lotion application. Use facial moisturizers as frequently as desired *[see Warnings and Precaution (5.2)]*.

Tazarotene cream is for topical use only. Tazarotene cream is not for ophthalmic, oral, or intravaginal use.

Use effective sunscreens and wear protective clothing while using tazarotene cream *[see Warnings and Precaution (5.3)]*.

2.3 Dosage and Administration Instructions

Remove any makeup before applying tazarotene cream to the face. Dry the skin before applying the cream after face washing, bathing, or showering.

Apply a pea-sized amount once a day at bedtime to lightly cover the entire face, including the eyelids, if desired.

Wash hands thoroughly after application.

3 DOSAGE FORMS AND STRENGTHS

Cream: 1 mg of tazarotene per gram (0.1%) of white cream in 30 gram tubes.

4 CONTRAINDICATIONS

Tazarotene cream is contraindicated in :

- Pregnancy. Retinoids may cause fetal harm when administered to a pregnant female *[see Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)]*.
- Individuals who have known hypersensitivity to any of its components *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryofetal Toxicity

Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, tazarotene cream may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk

to the fetus outweighs the potential benefit to the mother from tazarotene cream use during pregnancy; therefore, discontinue tazarotene cream as soon as pregnancy is recognized. Tazarotene elicits malformations and developmental effects associated with retinoids after topical and oral administration to pregnant rats and rabbits during organogenesis. However, limited case reports of pregnancy in females enrolled in clinical trials for tazarotene cream have not reported a clear association with tazarotene and major birth defects or miscarriage risk *[see Contraindications (4), Use in Specific Populations (8.1)]*.

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 as in these orally treated animals. Although there may be less systemic exposure in the treatment of the face alone due to less surface area for application, tazarotene is a teratogenic substance in animals, and it is not known what level of exposure is required for teratogenicity in humans *[see Clinical Pharmacology (12.3)]*.

Advise pregnant females of the potential risk to a fetus. Obtain a pregnancy test within 2 weeks prior to tazarotene cream therapy. Initiate tazarotene cream therapy during a menstrual period. Advise females of reproductive potential to use effective contraception during treatment with tazarotene cream *[see Dosage and Administration (2), Use in Specific Populations (8.3)]*.

5.2 Local Irritation and Hypersensitivity Reactions

Local tolerability reactions (including blistering and skin desquamation) and hypersensitivity adverse reactions (including urticaria) have been observed with topical tazarotene. Application of tazarotene cream may cause excessive irritation in the skin of certain sensitive individuals. Some individuals may experience excessive pruritus, burning, skin redness, or peeling. If these adverse reactions occur, discontinue the medication until the integrity of the skin is restored, or reduce the dosing to an interval the patient can tolerate. Closely monitor the frequency of application by carefully observing the therapeutic response and skin tolerance.

Avoid concomitant use of topical medications and cosmetics that have a strong drying effect. It is also advisable to “rest” a patient's skin until the effects of such preparations subside before use of tazarotene cream is begun.

Avoid using tazarotene cream on eczematous skin because such use may cause severe irritation.

Weather extremes, such as wind or cold, may be more irritating to patients using tazarotene cream.

5.3 Photosensitivity and Risk of Sunburn

Because of heightened burning susceptibility, minimize exposure to ultraviolet rays (including sunlight and sun lamps) during the use of tazarotene cream. Patients must be warned to use sunscreens and protective clothing when using tazarotene cream. Advise patients with sunburn not to use tazarotene cream until the sunburn is fully recovered.

Patients who may have considerable sun exposure because of their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using tazarotene cream.

Avoid using tazarotene cream 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.

5.4 Lentigo Maligna

Some facial pigmented lesions are not lentigines, but rather lentigo maligna, a type of melanoma. Before application of tazarotene cream, carefully assess facial pigmented lesions of concern by a qualified physician (e.g., dermatologist) to exclude a diagnosis of lentigo maligna.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of the labeling:

- Embryofetal toxicity *[see Warnings and Precautions (5.1)]*
- Photosensitivity and Risk of Sunburn *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

The most frequent adverse reactions reported with tazarotene cream, 0.1% that occurred in greater than 10% of subjects, included desquamation, erythema, burning sensation, and dry skin (in descending order). Reactions that occurred in 1 to 10% of subjects, included skin irritation, pruritus, irritant contact dermatitis, stinging, rash, and cheilitis (in descending order). Common adverse events that occurred at a rate of at least 1% and at a higher rate in the tazarotene cream group than in the vehicle group in the clinical trials are presented in the following table.

TABLE OF ADVERSE EVENTS SEEN IN 24-WEEK CLINICAL TRIALS WITH TAZAROTENE CREAM, 0.1%

Adverse Event	**Tazarotene N=567**	**Vehicle N=564**
Desquamation	40%	3%
Erythema	34%	3%
Burning Sensation	26%	<1%
Dry Skin	16%	3%
Irritation Skin	10%	1%
Pruritus	10%	1%
Irritant Contact Dermatitis	8%	1%
Stinging	3%	<1%
Rash	3%	1%
Cheilitis	1%	0%

A few subjects reported adverse events at Week 0; however, for patients who were treated with tazarotene cream, the highest number of new reports for each adverse event was at Week 2.

When combining data from the two trials, 5.3% of subjects in the tazarotene cream group and 0.9% of subjects in the vehicle group discontinued because of adverse events.

Overall, 20/567 (3.5%) subjects in the tazarotene cream group and 16/564 (2.8%) subjects in the vehicle group reported adverse events (including edema, irritation, and inflammation) directly related to the eye or eyelid. The majority of these conditions were mild.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of tazarotene. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: blister, dermatitis, urticaria, skin exfoliation, skin discoloration (including skin hyperpigmentation or skin hypopigmentation), swelling at or near application sites, and pain.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with tazarotene cream.

In a trial of 27 healthy female subjects between the ages of 20 to 55 years receiving a combination oral contraceptive tablet containing 1 mg norethindrone and 35 mcg ethinyl estradiol, concomitant use of tazarotene administered as 1.1 mg orally (mean ± SD C_{max} and AUC_{0-24} of tazarotenic acid were 28.9 ± 9.4 ng/mL and 120.6 ± 28.5 ng*h/mL) did not affect the pharmacokinetics of norethindrone and ethinyl estradiol over a complete cycle.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, tazarotene cream may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. Safety in pregnant females has not been established. The potential risk to the fetus outweighs the potential benefit to the mother from tazarotene cream during pregnancy; therefore, tazarotene cream should be discontinued as soon as pregnancy is recognized *[see Contraindications (4), Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*. Limited case reports of pregnancy in females enrolled in clinical trials for tazarotene cream have not established a clear association with tazarotene and major birth defects or miscarriage risk. Because the exact timing and extent of exposure in relation to the gestational age are not certain, the significance of these findings is unknown.

In animal reproduction studies with pregnant rats, tazarotene dosed topically during organogenesis at 2 times the maximum systemic exposure in subjects treated with the maximum recommended human dose (MRHD) of tazarotene cream, 0.1% resulted in reduced fetal body weights and reduced skeletal ossification. In animal reproduction studies with pregnant rabbits dosed topically with tazarotene gel at 26 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%, there was a single incident of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

In animal reproduction studies with pregnant rats and rabbits, tazarotene dosed orally during organogenesis at 2 and 52 times, respectively, the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1% resulted in malformations, fetal toxicity, developmental delays, and/or behavioral delays. In pregnant rats, tazarotene dosed orally prior to mating through early gestation resulted in decreased litter size, decreased numbers of live fetuses, decreased fetal body weights, and increased malformations at doses approximately 7 times higher than the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1% *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In rats, a tazarotene 0.05% gel formulation dosed topically during gestation days 6 through 17 at 0.25 mg/kg/day, which represented 2 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1% (*i.e.*, 2 mg/cm^2 over a 15% body surface area), resulted in reduced

fetal body weights and reduced skeletal ossification. Rabbits dosed topically with 0.25 mg/kg/day tazarotene gel, which represented 26 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%, during gestation days 6 through 18, had a single incident of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies.

When tazarotene was given orally to animals, developmental delays were seen in rats, and malformations and post-implantation loss were observed in rats and rabbits at doses representing 2 and 52 times, respectively, the maximum systemic exposure seen in subjects treated with the MRHD of tazarotene cream, 0.1%.

In female rats orally administered 2 mg/kg/day of tazarotene from 15 days before mating through gestation day 7, which represented 7 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%, classic developmental effects of retinoids were observed including decreased number of implantation sites, decreased litter size, decreased numbers of live fetuses, and decreased fetal body weights. A low incidence of retinoid-related malformations was observed at that dose.

In a pre- and postnatal development toxicity study, topical administration of tazarotene gel (0.125 mg/kg/day) to pregnant female rats from gestation day 16 through lactation day 20 reduced pup survival, but did not affect the reproductive capacity of the offspring. Based on data from another study, the maximum systemic exposure in the rat would be equivalent to the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%.

8.2 Lactation

Risk Summary

There is no information regarding the presence of tazarotene in human milk, the effects on the breastfed infant, or the effects on milk production. After single topical doses of ^{14}C-tazarotene gel to the skin of lactating rats, radioactivity was detected in rat milk. The lack of clinical data during lactation precludes a clear determination of the risk of tazarotene cream to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tazarotene cream and any potential adverse effects on the breastfed child from tazarotene cream or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential within 2 weeks prior to initiating tazarotene cream therapy which should begin during a menstrual period.

Contraception

Females

Based on animal studies, tazarotene cream may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with tazarotene cream.

8.4 Pediatric Use

The safety and efficacy of tazarotene cream have not been established in patients under the age of 17 years with facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines.

8.5 Geriatric Use

In the studies of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines, 44 male subjects and 180 female subjects out of the total population of 1131 subjects were

older than 65 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

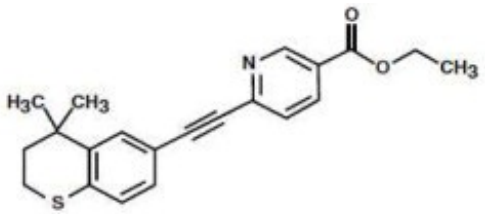
10 OVERDOSAGE

Tazarotene cream is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, monitor the patient closely and administer appropriate supportive measures, as necessary.

11 DESCRIPTION

Tazarotene cream, 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of tazarotene cream, 0.1% contains 1 mg of tazarotene in a white cream base.

Tazarotene is a member of the acetylenic class of retinoids. Chemically, tazarotene is ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl] nicotinate. The compound has an empirical formula of $C_{21}H_{21}NO_2S$ and molecular weight of 351.46. The structural formula is shown below:



TAZAROTENE

Tazarotene cream contains the following inactive ingredients: benzyl alcohol 1%, carbomer 974P; carbomer 1342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium thiosulfate, sorbitan monooleate, and sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tazarotene is a retinoid prodrug which is converted to its active form, the carboxylic acid of tazarotene, by deesterification. Tazarotenic acid binds to all three members of the retinoic acid receptor (RAR) family: RARα, RARβ, and RARγ, but shows relative selectivity for RARβ and RARγ, and may modify gene expression. The clinical significance of these findings for the mitigation of facial fine wrinkling, facial mottled hyper-and hypopigmentation, and benign facial lentigines is unknown.

12.3 Pharmacokinetics

Following topical application, tazarotene undergoes esterase hydrolysis to form its active metabolite, tazarotenic acid. Little parent compound could be detected in the plasma. Tazarotenic acid was highly bound to plasma proteins (greater than 99%). Tazarotene and tazarotenic acid were metabolized to sulfoxides, sulfones, and other polar metabolites which were eliminated through urinary and fecal pathways. The half-life of tazarotenic acid was approximately 18 hours.

Tazarotene cream, 0.1% was topically applied once daily over four weeks to either the face (6 females and 2 males) or to 15% of body surface area (8 females and 8 males) in subjects with fine wrinkling and

mottled hyperpigmentation. In the “face-only” dosing group, the maximum average C_{max} and AUC_{0-24hr} values of tazarotenic acid occurred on Day 15 with mean ± SD values of C_{max} and AUC_{0-24hr} of tazarotenic acid being 0.236 ± 0.255 ng/mL (N=8) and 2.44 ± 1.38 ng·hr/mL (N=8), respectively. The mean C_{max} and AUC_{0-24hr} values of tazarotenic acid from subjects in the 15% body surface area dosing group were approximately 10 times higher than those from subjects in the face-only dosing group. The single highest C_{max} throughout the trial period was 3.43 ng/mL on day 29 from subjects in the 15% body surface area dosing group. Gender had no influence on the systemic bioavailability of tazarotenic acid.

Blood samples were collected from one of the two phase 3 trials to evaluate the systemic exposure following application of tazarotene cream, 0.1% once daily for 24 weeks (double-blind period) followed by 28 weeks (open-label) under clinical conditions. The mean plasma tazarotenic acid concentrations, following topical treatment with tazarotene cream, 0.1% over 52 weeks, ranged between 0.092 ± 0.073 ng/mL and 0.127 ± 0.142 ng/mL. The single highest observed tazarotenic acid concentration throughout the 52-week trial was 0.705 ng/mL (observed at week 36). Systemic availability of tazarotenic acid was minimal and remained steady following once daily application of tazarotene cream, 0.1% to the faces of subjects in the trial for up to 52 weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%.

A long-term topical application study of up to 0.1% 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. Systemic exposure at the highest dose represented 8 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%.

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

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 tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1 mg/kg/day tazarotene, which represented 4 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1%.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose, which represented 7 times the maximum systemic exposure in subjects treated with the MRHD of tazarotene cream, 0.1% *[see Use in Specific Populations (8.1)]*.

14 CLINICAL STUDIES

Two double-blind, randomized vehicle-controlled trials (Trial 1 and Trial 2) enrolled 1131 subjects with mild to severe fine wrinkling, facial mottled hyper- and hypo-pigmentation, and benign facial lentigines because of sun overexposure. Both trials compared the application of tazarotene cream, 0.1% to its vehicle once daily for 24 weeks to the facial skin. Treatment was as an adjunct to a comprehensive skin care and sun avoidance program that included use of sunscreens, protective clothing, and non-prescription emollient cream.

In both trials, the endpoint was the proportion of subjects achieving an improvement of at least one grade from baseline in fine wrinkling, mottled hypo- and hyper-pigmentation, and benign facial lentigines. At two to four week intervals, the severity of fine wrinkling, mottled hyper- and hypo-pigmentation, and benign facial lentigines were graded using a 5-point photonumeric scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe).

Of 1131 subjects, approximately 97% of subjects in clinical trials were white (Caucasian) with 80% of subjects in the clinical studies having Fitzpatrick skin type classifications I-III. The distribution of subject skin types were: Type I –12%; Type II – 26%; Type III – 40%; and Type IV-22%. Subjects with skin types V and VI were not studied. Insufficient number of non-white subjects (Asian, Hispanic, or other) were studied to make an adequate determination of efficacy of tazarotene cream in such subjects.

Percentage of Subjects with Improvement in Fine Wrinkling after 24 Weeks of Treatment

	Trial 1		Trial 2	
	Tazarotene Cream, 0.1% N=283	Vehicle N=280	Tazarotene Cream, 0.1% N=284	Vehicle N=284
2 or more Grades Improvement	5%	1%	13%	5%
1 Grade Improvement	35%	15%	45%	18%
No Change	59%	83%	42%	76%
Worsened	1%	1%	0%	1%

Fine Wrinkling was graded on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) using a photonumeric guideline for investigators.

Percentage of Subjects with Improvement in Mottled Hyperpigmentation after 24 Weeks of Treatment

	Trial 1		Trial 2	
	Tazarotene Cream, 0.1% N=283	Vehicle N=280	Tazarotene Cream, 0.1% N=284	Vehicle N=284
2 or more Grades Improvement	17%	1%	28%	10%
1 Grade Improvement	42%	17%	54%	30%
No Change	41%	80%	18%	59%
Worsened	<1%	3%	<1%	1%

Mottled hyperpigmentation was graded on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) using a photonumeric guideline for investigators.

In the 24 week trials, efficacy was also demonstrated in mottled hypopigmentation and benign facial lentigines, which were secondary endpoints in those trials.

The duration of the mitigating effects on facial fine wrinkling, mottled hyper- and hypopigmentation, and benign facial lentigines following discontinuation of tazarotene cream has not been studied.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tazarotene cream, 0.1%, containing 1 mg of tazarotene per gram of white cream is available in a 30 gram collapsible aluminum tube with a tamper-evident aluminum membrane over the opening and a white polypropylene screw cap

(NDC 0168-0455-30).

Storage: Store at 25°C (77°F). Excursions permitted from -5°C to 30°C (23° F to 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Embryofetal Toxicity

Inform females of reproductive potential of the potential risk to a fetus. Advise these patients to use effective contraception during treatment with tazarotene cream. Advise patients to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)]*.

Photosensitivity and Risk of Sunburn

Advise patients to avoid excessive sun exposure and to use sunscreens and protective measures (hat, visor). Advise patients to avoid using tazarotene cream if also taking other medicines that may increase sensitivity to sunlight.

Important Administration Instructions

Advise patients of the following:

1. Use tazarotene cream on the face once per day, at bedtime.
2. Tazarotene cream is for topical use only. Do not apply to eyes, mouth, or other mucous membranes. The cream may cause severe redness, itching, burning, stinging, and peeling. Avoid accidental transfer of tazarotene cream into eyes, mouth, or other mucous membranes. If contact with mucous membranes occurs, rinse thoroughly with water. Seek medical attention if eye irritation continues. Wash hands thoroughly after applying tazarotene cream.
3. Gently wash face with a mild soap before applying the cream.
4. Dry skin before applying the cream.
5. Apply only a small pea sized amount (about 1/4 inch or 5 millimeter diameter) to lightly cover the entire face.
6. Apply emollients or moisturizers before or after tazarotene cream and ensure that the first cream or lotion has absorbed into the skin and dried completely.
7. In the morning, apply a moisturizing sunscreen.

Manufactured by:

E. FOUGERA & CO.

A division of Fougera Pharmaceuticals Inc.

Melville, New York 11747

For more information call 1-800-645-9833.

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R09/18

PATIENT INFORMATION

TAZAROTENE
(tah-ZAR-oh-teen**)**
Cream, 0.1%

Important information: Tazarotene cream is for use on skin only. Do not use tazarotene cream in your eyes, mouth, or vagina.

What is the most important information I should know about tazarotene cream?
Tazarotene cream may cause birth defects if used during pregnancy.

- **Females must not be pregnant when they start using tazarotene creamor become pregnant during treatment with tazarotene cream.**
- For females who are able to get pregnant:
  - Your doctor will order a pregnancy test for you within 2 weeks before you begin treatment with tazarotene cream to be sure that you are not pregnant. Your doctor will decide when to do the test.
  - Begin treatment with tazarotene cream during a normal menstrual period.
  - Use an effective form of birth control during treatment with tazarotene cream. Talk with your doctor about birth control options that may be used to prevent pregnancy during treatment with tazarotene cream.
  - **Stop using tazarotene creamand tell your doctor right away if you become pregnant while using tazarotene cream.**

What is tazarotene cream?
Tazarotene cream is a prescription medicine used on the skin (topical) that may reduce fine facial wrinkles and certain types of dark and light spots on the face in people who use a total skin care program and avoid sunlight.

- Tazarotene cream does not remove or prevent wrinkles, repair sun damaged skin, reverse skin aging from the sun (photoaging), or bring back more youthful or younger skin.
- Tazarotene cream does not work for everyone who uses it. It may work better for some people than for others.
- It is not known if tazarotene cream is safe and effective for the prevention or treatment of certain other skin problems.
- It is not known if tazarotene cream is safe and effective in children under 17 years of age with facial fine wrinkles and certain types of dark and light spots on the face.

Who should not use tazarotene cream?
Do not use tazarotene cream if you:

- are pregnant or plan to become pregnant. See “What is the most important information I should know about tazarotene cream?” at the beginning of this leaflet.
- are allergic to tazarotene or any of the ingredients in tazarotene cream. See the end of this leaflet for a complete list of ingredients in tazarotene cream.

What should I tell my doctor before using tazarotene cream?
Before you use tazarotene cream, tell your doctor about all of your medical conditions, including if you:

- have eczema or any other skin problems, including skin cancers
- are breastfeeding or plan to breastfeed. It is not known if tazarotene cream passes into your breast milk. Talk to your doctor about using tazarotene cream while breastfeeding.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Certain medicines, vitamins, or supplements may make your skin more sensitive to sunlight. Also, tell your doctor about any cosmetics you use, including moisturizers, creams, lotions, or products that can dry out your skin.

How should I use tazarotene cream?

- Use tazarotene cream exactly as your doctor tells you to use it.
- Apply tazarotene cream 1 time a day, at bedtime.
- Do not get tazarotene cream in your eyes. If tazarotene cream gets in your eyes, rinse them well with water. Call your doctor or get medical help if you have eye irritation that does not go away.
- Wash your hands after applying tazarotene cream.

Follow these instructions for applying tazarotene cream:

- Gently wash your face with mild soap. Be sure to remove any makeup. Rinse and pat your skin dry.
- Apply a pea-sized amount to lightly cover your face. You can include your eyelids, if desired.
- In the morning, apply a moisturizing sunscreen.
- You can use a cream or lotion to soften or moisten your skin before or after you apply tazarotene cream. Make sure that the first cream or lotion has absorbed into your skin and dried completely before you apply the second product.
- You can use facial moisturizers, such as lotions, oils, and creams, as often as you want.
- If you swallow tazarotene cream, call your doctor or go to the nearest emergency room right away.

What should I avoid while using tazarotene cream?

- Avoid sunlight, including sunlamps, during treatment with tazarotene cream. Tazarotene cream can make you more sensitive to the sun, and the light from sunlamps and tanning beds. You could get a severe sunburn. Use sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.
- Talk to your doctor if you get a sunburn during treatment with tazarotene cream. If you get a sunburn, do not use tazarotene cream until your sunburn is healed.
- Avoid using cosmetics or topical medicines that may make your skin more sensitive to sunlight or make your skin dry.
- Avoid using tazarotene cream on skin with eczema because it may cause severe irritation.

What are the possible side effects of tazarotene cream?
Tazarotene creammay cause serious side effects, including:

- **Skin irritation and allergic reactions (hypersensitivity).** Tazarotene cream may cause increased skin irritation and hives. Tell your doctor if you develop hives, or itching, burning, redness, or peeling of your skin during treatment with tazarotene cream. If you develop hives or skin irritation, your doctor may tell you to stop using tazarotene cream until your skin heals or tell you to use tazarotene cream less often. Also, wind or cold weather may be more irritating to your skin while you are using tazarotene cream.
- **Sensitivity to sunlight and risk of sunburn.** See “What should I avoid while using tazarotene

cream?”

The most common side effects of tazarotene cream include peeling, redness, burning, dry or irritated skin, and itching.
These are not all the side effects possible of tazarotene cream. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store tazarotene cream?

- Store tazarotene cream at 77°F (25°C).
- Keep tazarotene cream and all medicines out of the reach of children.

General information about the safe and effective use of tazarotene cream.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use tazarotene cream for a condition for which it was not prescribed. Do not give tazarotene cream to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about tazarotene cream that is written for health professionals.

What are the ingredients of tazarotene cream?
Active ingredient: tazarotene
Inactive ingredients: benzyl alcohol, carbomer 974P, carbomer 1342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium thiosulfate, sorbitan monooleate and sodium hydroxide to adjust pH.

Manufactured by:
E. FOUGERA & CO.
A division of Fougera Pharmaceuticals Inc.
Melville, New York 11747
For more information call 1-800-645-9833.
46218957A
R09/18

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: September 2018

NDC 0168-0455-30 **Rx Only**

Tazarotene Cream, 0.1%

NET WT 30 grams

For Topical Use Only
Not for Ophthalmic Use

Fougera®

Package/Label Display Panel

NDC 0168-0455-30

Tazarotene Cream, 0.1%

NET WT 30 grams

Fougera®

NDC 0168-0455-30

℞ only

Tazarotene Cream, 0.1%

NET WT 30 grams

fougera®

Active Ingredient: Tazarotene 0.1% (w/w)

Preservative: Benzyl alcohol 1% (w/w)

Inactive Ingredients: carbomer 974P, carbomer 1342, edetate disodium, medium chain triglycerides, mineral oil, purified water, sodium thiosulfate, sorbitan monooleate, and sodium hydroxide to adjust pH.

Usual Dosage: Refer to accompanying patient leaflet and complete prescribing information.

Manufactured by: E. FOUGERA & CO., A division of Fougera Pharmaceuticals Inc. Melville, New York 11747

46218955A R02/18

This product is sealed for your protection. If the seal is broken or missing return to place of purchase.

TO OPEN: To puncture the seal, reverse the cap and place the puncture-top onto the tube. Push down firmly until seal is open. To close, screw the cap back onto the tube.

For Topical Use Only

Not for Ophthalmic Use

Store at 25°C (77°F). Excursions permitted from -5°C to 30°C (23° F to 86°F).

KEEP OUT OF THE REACH OF CHILDREN.

See crimp of tube for Lot No. and Exp. Date.

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TAZAROTENE CREAM

tazarotene cream

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0168-0455
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
tazarotene (UNII: 81BDR9Y8PS) (tazarotene - UNII:81BDR9Y8PS)	tazarotene	1 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
benzyl alcohol (UNII: LKG8494WBH)	
carbomer homopolymer type B (allyl pentaerythritol crosslinked) (UNII: HHT01ZNK31)	
CARBOMER COPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED) (UNII: 809Y72KV36)	
edetate disodium (UNII: 7FLD91C86K)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	
mineral oil (UNII: T5L8T28FGP)	
water (UNII: 059QF0KO0R)	
sodium thiosulfate (UNII: HX1032V43M)	
sorbitan monooleate (UNII: 06XEA2VD56)	

sodium hydroxide (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0168-0455-30	1 in 1 CARTON	01/28/2019	
1		30 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA211175	01/28/2019	

Labeler - E. Fougera & Co. a division of Fougera Pharmaceuticals Inc. (043838424)

Establishment

Name	Address	ID/FEI	Business Operations
Particle Technology Labs		808076947	ANALYSIS(0168-0455)

Revised: 9/2020 E. Fougera & Co. a division of Fougera Pharmaceuticals Inc.