

TRETINOIN- tretinoin gel

Amneal Pharmaceuticals NY LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRETINOIN GEL (MICROSPHERE) safely and effectively. See full prescribing information for TRETINOIN GEL (MICROSPHERE).

TRETINOIN gel (microsphere), for topical use
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

Tretinoin gel (microsphere) is a retinoid indicated for the topical treatment of acne vulgaris in adults and pediatric patients 12 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- For topical use only. Not for oral, ophthalmic, or intravaginal use. (2)
- Keep away from eyes, mouth, paranasal creases of the nose, and mucous membranes. (2)
- Apply a thin layer of tretinoin gel (microsphere) to skin where acne lesions appear (cover the entire affected area) once daily in the evening. (2)

DOSAGE FORMS AND STRENGTHS

Gel, 0.08% (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Local Skin Irritation:** Tretinoin gel can cause local skin irritation, including excessive dryness, redness, swelling, peeling, itching, blistering, burning, or stinging (5.1)
 - Avoid use on eczematous skin or during weather extremes, such as severe wind or cold.
 - To reduce the risk of local skin irritation, wash the treated skin gently, using a mild, non-medicated soap, avoid washing the treated skin too often or scrubbing it hard when washing, and apply a topical moisturizer.
 - If severe local skin irritation occurs, discontinue use temporarily or permanently.
- **Initial Worsening of Inflammatory Acne Vulgaris:** During the early weeks of tretinoin gel treatment, an apparent exacerbation of inflammatory lesions may occur. If tretinoin gel is tolerated, this should not be considered a reason to discontinue therapy. (5.2)
- **Photosensitivity:** Tretinoin gel can cause photosensitivity. Advise patients to avoid or minimize unnecessary exposure to UV light, including sunlight and sunlamps. Advise patients to use sunscreen (SPF \geq 15) and sun-protective clothing if UV light exposure cannot be avoided. Avoid use on sunburn skin. (5.3)

ADVERSE REACTIONS

Most common adverse reactions were skin irritation, skin burning, erythema, peeling, dryness, itching, and dermatitis. (6.1)

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

USE IN SPECIFIC POPULATIONS

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Local Skin Irritation

5.2 Initial Worsening of Inflammatory Acne Vulgaris

5.3 Photosensitivity

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Clinical Studies of Tretinoin Gel, 0.1%

14.2 Clinical Studies with Tretinoin Gel, 0.04%

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tretinoin gel (microsphere) is indicated for the topical treatment of acne vulgaris in adults and pediatric patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

For topical use only. Not for oral, ophthalmic, or intravaginal use.

- Prior to tretinoin gel (microsphere) use, thoroughly cleanse area(s) with a mild, non-medicated cleanser then pat the skin dry.
- When applying tretinoin gel (microsphere), keep away from the eyes, the mouth, paranasal creases of the nose, and mucous membranes.

- Apply a thin layer of tretinoin gel (microsphere), 0.08% to skin where acne lesions appear (cover the entire affected area), once daily in the evening. Do not apply more than a thin layer [*see Warning and Precautions (5.1)*].

Improvements in acne lesions may be noticed after two weeks of tretinoin gel (microsphere) therapy, but more than seven weeks of therapy may be needed for sustained benefit.

If tretinoin gel (microsphere) was temporarily discontinued due to local adverse reactions, tretinoin gel (microsphere) therapy may be resumed upon resolution of local adverse reactions.

3 DOSAGE FORMS AND STRENGTHS

Tretinoin gel, USP (microsphere), 0.08% is a white to very pale-yellow opaque gel. Tretinoin gel, USP is available in one strength: 0.08%.

Each gram of tretinoin gel, USP (microsphere), 0.08%, contains 0.8 mg of tretinoin, USP.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Skin Irritation

Tretinoin gel can cause local skin irritation, including excessive dryness, redness, swelling, peeling, itching, blistering, burning, or stinging [*see Adverse Reactions (6.1)*]. Use of tretinoin gel in greater than the recommended dosage (more frequent than once daily application or excessive application) will not result in more rapid or improved acne results and may result in marked redness, peeling, or discomfort.

Tretinoin has been reported to cause severe local skin irritation on eczematous skin.

Weather extremes, such as severe wind or cold, may increase the risk of skin irritation in patients using tretinoin gel.

To reduce the risk of local skin irritation, instruct tretinoin gel treated patients to:

- Avoid use of tretinoin gel in areas affected by eczema.
- Minimize or avoid use of tretinoin gel with weather extremes.
- Wash the treated skin gently, using a mild, non-medicated soap, pat it dry, and avoid washing the treated skin too often or scrubbing it hard when washing. Tretinoin gel is not recommended with concomitant use of medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, spices, or lime peels.
- Apply a topical moisturizer.

Advise patients that concomitant use of topical over the counter (OTC) acne products containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with tretinoin gel may increase the risk for local skin irritation including dryness, erythema, and peeling.

Consider withholding the use of topical OTC acne products if signs of skin irritation develop. Advise patients to allow the skin irritation effects of the topical OTC acne products to subside before initiation of tretinoin gel treatment.

If severe local skin irritation occurs, discontinue tretinoin gel use temporarily or permanently.

Efficacy of tretinoin gel at reduced frequencies of application has not been established.

5.2 Initial Worsening of Inflammatory Acne Vulgaris

During the early weeks of tretinoin gel treatment, an apparent exacerbation of inflammatory acne vulgaris lesions may occur. If tretinoin gel is tolerated, initial worsening of inflammatory acne vulgaris lesions should not be considered a reason to discontinue therapy.

5.3 Photosensitivity

Tretinoin gel can cause photosensitivity. Advise patients to avoid or minimize unnecessary exposure to ultraviolet (UV) light, including sunlight and sunlamps, while using tretinoin gel. Advise patients with sunburn to not use tretinoin gel until the sunburn fully recovers.

Advise patients, especially those who may be required to have extended periods of UV light exposure (e.g., due to occupation or sports), those with inherent sensitivity to the sun, or those using drugs that cause photosensitivity, to use sun protection daily in the form of sunscreen (sun protection factor [SPF] ≥ 15) and sun-protective clothing, when UV exposure cannot be avoided, even on days when it is not sunny or inside activities are expected.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Tretinoin gel, 0.1%

The safety of tretinoin gel, 0.1% for the treatment of acne vulgaris was evaluated in two multicenter, double-blind, randomized, vehicle-controlled clinical trials (Studies 1 and 2). A total of 347 subjects with acne vulgaris were treated in Studies 1 and 2 in which 172 subjects received tretinoin gel, 0.1% and 175 subjects received vehicle, applied topically once daily in the evening, for 12 weeks. Mean age was 19 years (range 11 to 40) and 55% were female [see *Clinical Studies (14.1)*]. Tretinoin gel is not approved for use in pediatric patients younger than 12 years of age [see *Indications and Usage (1)*].

In Studies 1 and 2, subjects treated with tretinoin gel, 0.1% had increased cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or itching that peaked during the initial two weeks of therapy and decreased thereafter, compared to those treated with vehicle [see *Warnings and Precautions (5.1)*]. During the 12-week treatment period, no more than 3% of tretinoin gel, 0.1%-treated subjects had cutaneous irritation

scores indicative of severe cutaneous irritation and 6% (14/224) of tretinoin gel, 0.1%-treated subjects discontinued treatment due to cutaneous irritation. Of these 14 subjects, four had severe cutaneous irritation after 3 to 5 days of treatment, with blistering in one subject.

Tretinoin gel, 0.04%

The safety of tretinoin gel, 0.04% for the treatment of acne vulgaris was evaluated in two multicenter, double-blind, randomized, vehicle-controlled clinical trials (Studies 3 and 4). A total of 451 subjects with acne vulgaris were treated in Studies 3 and 4 in which 225 subjects received tretinoin gel, 0.04% and 226 subjects received vehicle, applied once daily in the evening, for 12 weeks. Mean age was 19 years (range 11 to 49) and 57% were female [see *Clinical Studies (14.2)*]. Tretinoin gel is not approved for use in pediatric patients younger than 12 years of age [see *Indications and Usage (1)*].

In Studies 3 and 4, subjects treated with tretinoin gel, 0.04% had increased cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or itching that peaked during the initial two weeks of therapy and decreased thereafter, compared to those treated with vehicle [see *Warnings and Precautions (5.1)*].

Approximately half of the 225 subjects in the tretinoin gel, 0.04%-treated group had cutaneous irritation at Week 2. Of the subjects who experienced cutaneous irritation, most had signs or symptoms that were mild in severity (severity was ranked on a 4-point ordinal scale: 0=none, 1=mild, 2=moderate, and 3=severe). Less than 10% of tretinoin gel, 0.04%-treated subjects experienced moderate cutaneous irritation, and none had severe cutaneous irritation at Week 2.

In Studies 3 and 4, during the 12-week treatment period, the majority of tretinoin gel, 0.04%-treated subjects experienced cutaneous irritation (mild, moderate, or severe), of which, 1% (2/225) of subjects had cutaneous irritation scores indicative of a severe irritation and 1.3% (3/225) of subjects discontinued treatment due to cutaneous irritation, which included dryness in one subject and peeling and urticaria in another.

Tretinoin gel, 0.04% and 0.1%

In a double-blind trial, 156 subjects with acne vulgaris were treated for 12-weeks with tretinoin gel, 0.04% (n=78) or 0.1% (n=78) topically once daily. In this trial, the most frequently reported adverse events affected the skin and subcutaneous tissue (15% in the 0.04% group, and 21% in the 0.1% group). The most prevalent events in the 0.04% group were skin irritation (6%); and in the 0.1% group, skin burning (8%), erythema (5%), skin irritation (4%), and dermatitis (4%). In this trial, 63% of the adverse events were of mild intensity, and 34% were of moderate intensity.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tretinoin gel and other topical tretinoin products. 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.

- Hyper- or hypopigmentation has been reported with repeated application of tretinoin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published prospective observational studies and retrospective cohort studies over decades of use of topical tretinoin in pregnant women have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (*see Data*).

In animal reproduction studies with pregnant rats, alterations in the vertebrae and ribs of offspring were observed with daily topical dosing of 0.1% tretinoin gel (microsphere) during organogenesis at 5 to 10 times the maximum recommended human dose (MRHD). In animal reproduction studies with pregnant rabbits, fetal malformations, such as domed head and hydrocephaly, were observed in the offspring with daily topical dosing of 0.1% tretinoin gel (microsphere) during organogenesis at 10 to 19 times the MRHD [*see Data*].

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US 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

Human Data: Published data from prospective observational studies and retrospective cohort studies on the use of topical tretinoin products during pregnancy have not identified an association with topical tretinoin and major birth defects or miscarriage. The available studies have methodologic limitations, including potential misclassification of exposure, small sample size and in some cases, lack of physical exam by an expert in birth defects.

Animal Data: For purposes of comparison of the animal exposure to systemic human exposure, the MRHD applied topically is defined as 1 gram of tretinoin gel microsphere, 0.1%, applied daily to a 60 kg person (0.017 mg tretinoin/kg body weight).

Pregnant rats were treated with 0.1% tretinoin gel (microsphere) at daily dermal doses of 0.2, 0.5, and 1 mg/kg/day tretinoin on gestation days 6 to 15. Alterations were seen in the vertebrae and ribs of the affected offsprings at 0.5 mg/kg/day tretinoin, 5 to 10 times the MRHD based on body surface area (BSA) comparison.

Pregnant rabbits were treated with 0.1% tretinoin gel (microsphere) at daily dermal doses of 0.2, 0.5, and 1 mg/kg/day tretinoin on gestation days 7 to 19. Doses were administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. Increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species were observed at doses of 0.5 and 1 mg/kg/day. Similar malformations were not observed in the offspring at 0.2 mg/kg/day, 4 times the MRHD based on BSA comparison. In a second rabbit study, pregnant rabbits were treated with 0.1% tretinoin gel (microsphere) at daily dermal doses of 0.5 or 1 mg/kg/day tretinoin on gestation days 7 to 19. Doses were administered topically for six hours per day while pregnant rabbits were restrained in stocks to prevent ingestion. The offspring of pregnant rabbits exposed to 0.5 or 1 mg/kg/day tretinoin did not show any malformations at doses up to

19 times (1.0 mg/kg/day) the MRHD based on BSA comparison, but fetal resorptions were increased at 0.5 mg/kg (10 times the MRHD based on BSA comparison).

Malformations (shortened or kinked tail) were observed in the offspring of pregnant rats treated with topical tretinoin at doses greater than 1 mg/kg/day during the period of organogenesis (10 times the MRHD based on BSA comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported in offspring when 10 mg/kg/day was topically applied to pregnant rats during the period of organogenesis. Supernumerary ribs have been a consistent finding in newborn rats when dams were treated topically or orally with retinoids.

Oral administration of tretinoin during organogenesis has been shown to cause malformations in the offspring of rats, mice, rabbits, hamsters, and nonhuman primates. Fetal malformations and death were observed when tretinoin was orally administered to pregnant rats during organogenesis at doses greater than 1 mg/kg/day (10 times the MRHD based on BSA comparison). Fetal malformations were reported at doses of 10 mg/kg/day or greater when administered to pregnant cynomolgus monkeys, but none were observed at 5 mg/kg/day (95 times the MRHD based on BSA comparison), although increased skeletal variations were observed at all doses. Dose-dependent increases in embryoletality and abortion also were reported. Similar results have also been reported in pigtail macaques.

In peri- and postnatal development studies in rats with oral tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (19 times the MRHD based on BSA comparison).

Oral tretinoin has been shown to be fetotoxic in rats when administered at doses 24 times the MRHD based on BSA comparison.

Topical tretinoin has been shown to be fetotoxic in rabbits when administered at doses 10 times the MRHD based on BSA comparison.

8.2 Lactation

Risk Summary

There are no data on the presence of tretinoin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable quantities in human milk (*see Clinical Considerations*).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tretinoin gel and any potential adverse effects on the breastfed infant from the tretinoin gel or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the infant via human milk, during breastfeeding, use tretinoin gel on the smallest area of skin with acne and for the shortest duration possible. Advise breastfeeding women not to apply tretinoin gel directly to the nipple and areola to avoid direct infant exposure.

8.4 Pediatric Use

The safety and effectiveness of tretinoin gel for topical application for the treatment of

acne vulgaris have been established in pediatric patients aged 12 years and older [see *Clinical Studies (14)*]. The safety and effectiveness of tretinoin gel have not been established in pediatric patients younger than 12 years of age.

8.5 Geriatric Use

Clinical trials of tretinoin gel did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger adult subjects. Acne vulgaris is largely a disease of pediatric and young adult patients. Clinical studies of tretinoin gel did not include patients 65 years of age and older.

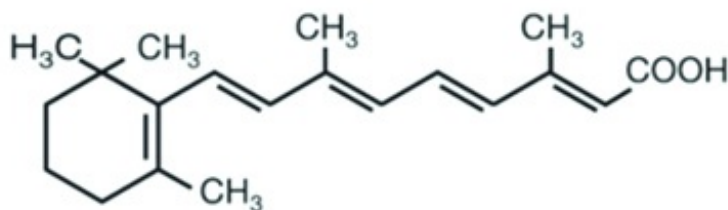
10 OVERDOSAGE

Oral ingestion of large amounts of tretinoin gel may lead to the same adverse reactions as those associated with excessive oral intake of Vitamin A.

Consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for overdose recommendations.

11 DESCRIPTION

Chemically, tretinoin, USP is all-trans-retinoic acid, also known as (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. Tretinoin, USP is a retinoid and a metabolite of naturally occurring Vitamin A. Tretinoin, USP has a molecular weight of 300.44, a molecular formula of $C_{20}H_{28}O_2$ and the following chemical structure:



Tretinoin gel, USP (microsphere) is for topical use. Each gram of tretinoin gel USP (microsphere), 0.08%, contains 0.8 mg of tretinoin, USP.

The formulation uses copolymer of methyl methacrylate and ethylene glycol dimethacrylate crosspolymer (microspheres system) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel. Other components consist of benzyl alcohol, butylated hydroxytoluene, carbomer 974P, cyclomethicone and PPG-18/18 dimethicone, disodium EDTA, glycerin, PPG-20 methyl glucose ether distearate, propylene glycol, purified water, sorbic acid, trolamine, and propylene glycol dicaprylate/dicaprate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although tretinoin activates three members of the retinoic acid (RAR) nuclear receptors

(RAR α , RAR β , and RAR γ) which may act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors and/or other mechanisms.

The exact mechanism of action of topical tretinoin for treatment of acne vulgaris is unknown. Current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedone formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

12.2 Pharmacodynamics

The pharmacodynamics of tretinoin gel is unknown.

12.3 Pharmacokinetics

Absorption

Tretinoin is a metabolite of Vitamin A. Percutaneous absorption, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in 44 healthy males and females after single and repeated daily tretinoin applications up to 28 days of 500 mg of a 0.1% tretinoin gel product. In this assessment, estimates of *in vivo* bioavailability, mean (SD) were 0.82 (0.11)% and 1.41 (0.54)%, for single and multiple daily topical applications, respectively. The plasma concentrations of tretinoin and its metabolites, 13- *cis*-retinoic acid, all- *trans*-4-oxo-retinoic acid, and 13- *cis*-4-oxo-retinoic acid, generally ranged from 1 to 3 ng/mL and were essentially unaltered after either single or multiple daily applications of tretinoin gel, 0.1%, relative to baseline levels.

Clinical pharmacokinetic studies have not been performed with tretinoin gel, 0.08%, 0.06% and 0.04%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dermal carcinogenicity testing has not been performed with tretinoin gel, 0.04%, 0.06%, 0.08%, or 0.1%.

In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of the 0.04% and 0.1% clinical formulations. A dose-dependent incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1 mg/kg/day tretinoin, respectively. These doses are two and four times the MRHD based on BSA comparison.

The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice.

There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was

administered topically to mice (0.1 times the MRHD based on BSA comparison). Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources [see *Warnings and Precautions (5.3)*].

The genotoxic potential of tretinoin was evaluated in the Ames assay and an *in vivo* mouse micronucleus assay. Both tests were negative.

The components of the microspheres have shown potential for genetic toxicity and fetal malformation. EGDMA, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in an *in vitro* chromosomal aberration assay in mammalian cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, and an *in vivo* mouse micronucleus assay.

In fertility studies in rats with oral tretinoin, the no-observable effect level was 2 mg/kg/day (19 times the MRHD based on BSA comparison).

14 CLINICAL STUDIES

14.1 Clinical Studies of Tretinoin Gel, 0.1%

The efficacy of tretinoin gel, 0.1 was evaluated in two double-blind, randomized, vehicle-controlled trials in adult and pediatric subjects 11 years of age and older with acne vulgaris (Studies 1 and 2). Tretinoin gel is not approved for use in pediatric patients younger than 12 years of age [see *Indications and Usage (1)*]. Tretinoin gel, 0.1%, applied topically once daily in the evening, was superior to vehicle gel, applied topically once daily, in reducing the acne lesion counts. The mean reduction in lesion counts from baseline after treatment for 12 weeks are shown in Table 1:

	Study 1		Study 2	
	Tretinoin Gel 0.1% (n=72)	Vehicle Gel (n=71)	Tretinoin Gel 0.1% (n=72)	Vehicle Gel (n=67)
Non-inflammatory lesion counts	49%	22%	32%	3%
Inflammatory lesion counts	37%	18%	29%	24%
Total lesion counts	45%	23%	32%	16%

Efficacy was also assessed by the investigator's global evaluation, which included categories of "excellent", "good", "fair", "no change", and "poor". Tretinoin gel, 0.1%, was significantly superior ($p < 0.001$) to the vehicle in the investigator's global evaluation of the clinical response:

- In Study #1, 35% of tretinoin gel, 0.1% -treated subjects achieved an "excellent" result, as compared to 11% of vehicle-treated subjects.
- In Study #2, 28% of tretinoin gel, 0.1%-treated subjects achieved an "excellent"

result, as compared to 9% of vehicle-treated subjects.

14.2 Clinical Studies with Tretinoin Gel, 0.04%

In two vehicle-controlled clinical trials in adult and pediatric subjects 11 years of age and older with acne vulgaris (Studies 3 and 4). Tretinoin gel is not approved for use in pediatric patients younger than 12 years of age [see *Indications and Usage (1)*]. Tretinoin gel, 0.04%, applied topically once daily in the evening, was more effective ($p < 0.05$) than vehicle gel, applied topically once daily, in reducing the acne lesion counts. The mean reduction in lesion counts from baseline after treatment for 12 weeks are shown in Table 2:

	Study 3		Study 4	
	Tretinoin Gel 0.04% (n=108)	Vehicle Gel (n=111)	Tretinoin Gel 0.04% (n=110)	Vehicle Gel (n=103)
Non-inflammatory lesion counts	37%	-2%	29%*	14%
Inflammatory lesion counts	44%	13%	41%	30%
Total lesion counts	40%	8%	35%	20%

* -2% represents a mean percent increase of 2%

Efficacy was also assessed by the investigator's global evaluation, which included categories of "excellent", "good", "fair", "no change", and "poor". Tretinoin gel, 0.04% was superior ($p < 0.05$) to the vehicle in the investigator's global evaluation of the clinical response:

- In Study #3, 14% of tretinoin gel, 0.04%-treated subjects achieved an "excellent" result, as compared to 5% of vehicle-treated subjects.
- In Study #4, 19% of tretinoin gel, 0.04%-treated subjects achieved an "excellent" result, as compared to 9% of vehicle-treated subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Tretinoin gel USP (microsphere), 0.08% is a white to very pale-yellow opaque gel; free from lumps and foreign matters filled in a black colored pump.

Tretinoin gel USP (microsphere), 0.08%, is supplied in 50 gram pump (NDC 69238-2323-1).

Storage and Handling

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

Store pump upright.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

Administration

Instruct the patient to *[see Dosage and Administration (2)]*:

- Thoroughly cleanse treatment area(s) with a mild, non-medicated cleanser then pat the skin dry prior to application of tretinoin gel.
- Avoid contact with eyes, mouth, paranasal creases of nose, and mucous membranes when applying tretinoin gel (microsphere).
- Apply a thin layer of tretinoin gel (microsphere) to cover the affected area(s).

Local Skin Irritation:

Advise the patient that use of tretinoin gel (microsphere) greater than the recommended dosage will not result in more rapid or improved acne results and may result in marked redness, peeling or discomfort *[see Warnings and Precautions (5.1)]*.

To reduce the risk of local skin irritation, advise the patient to:

- Minimize or avoid use of tretinoin gel (microsphere) during weather extremes, such as severe wind or cold.
- Wash the treated skin gently, using a mild, non-medicated soap, and pat it dry, and avoid washing the treated skin too often or scrubbing it hard when washing.
- Not use medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, spices, and lime peels while using tretinoin gel (microsphere).
- Apply a topical moisturizer when using tretinoin gel (microsphere).

Advise the patient that concomitant use of topical OTC acne products containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with tretinoin gel (microsphere) may increase the risk of local skin irritation. Advise the patient to withhold the use of topical OTC acne products if signs of skin irritation develop. Advise the patient to allow the skin irritation effects of the topical OTC acne products to subside before initiation of tretinoin gel (microsphere) *[see Warning and Precautions (5.1)]*.

Photosensitivity

Advise the patient to avoid or minimize unnecessary exposure to ultraviolet (UV) light, including sunlight and sunlamps, while using tretinoin gel (microsphere).

Advise the patient to not use tretinoin gel on sunburn skin.

Advise the patient to use sun protection in the form of sunscreen (SPF \geq 15) and sun-protective clothing if UV exposure cannot be avoided *[see Warnings and Precautions (5.3)]*.

Lactation

Advise the female patient to use tretinoin gel (microsphere) on the smallest area of skin with acne vulgaris and for the shortest duration possible while breastfeeding. To avoid

direct infant exposure, instruct the patient who is breastfeeding not to apply tretinoin gel (microsphere) directly to the nipple and areola [see *Use in Specific Populations (8.2)*].

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

Rev. 04-2026-01

Patient Information

Tretinoin (tret' i noyn) Gel, USP(microsphere)
for topical use

Important information: Tretinoin gel (microsphere) is for use on skin (topical use) only. Keep tretinoin gel (microsphere) away from your eyes, mouth, vagina, or the corners of your nose.

What is tretinoin gel (microsphere)?

Tretinoin gel (microsphere) is a prescription medicine used on the skin (topical) to treat acne in adults and children 12 years of age and older. Acne is a condition in which the skin has blackheads, whiteheads, and other pimples.

It is not known if tretinoin gel (microsphere) is safe and effective in children under 12 years of age.

Before using tretinoin gel (microsphere), tell your healthcare provider about all of your medical conditions, including if you:

- have a skin condition called eczema.
- have a sunburn. You should not use tretinoin gel (microsphere) until your skin has healed.
- are pregnant or plan to become pregnant. It is not known if tretinoin gel (microsphere) will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if tretinoin passes into your breast milk. If you breastfeed during treatment with tretinoin gel (microsphere), use tretinoin gel (microsphere) on the smallest area of the skin with acne and for the shortest time possible. Do not apply tretinoin gel (microsphere) directly to the nipple and areola to avoid contact with your baby.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you use any skin products that contain benzoyl peroxide, sulfur, resorcinol, or salicylic acid. Using these topical skin products may increase the irritation of your skin when used with tretinoin gel (microsphere).

How should I use tretinoin gel (microsphere)?

- Use tretinoin gel (microsphere) exactly as your healthcare provider tells you to use it.
- Before you apply tretinoin gel (microsphere), gently wash the affected skin area with a mild, non-medicated soap. Rinse and pat your skin dry.
- Apply a thin layer of tretinoin gel (microsphere) to the affected area 1 time a day in the evening.
- Do not use more tretinoin gel (microsphere) than you need to cover the affected area and do not apply tretinoin gel (microsphere) more than 1 time a day. Using too much tretinoin gel (microsphere) or using it too often will not give you faster or

better results, and you may get skin redness, peeling, or discomfort.

- You may use moisturizers after applying tretinoin gel (microsphere).
- Early in your treatment, you may get new pimples. At this stage, it is important to continue using tretinoin gel (microsphere).
- Your acne may not get better right away. Improvement in your acne may be noticed after 2 weeks of tretinoin gel (microsphere) treatment, but more than 7 weeks of treatment may be needed before you get the full benefit. Wash your hands after applying tretinoin gel (microsphere).
- Tretinoin gel (microsphere) taken by mouth in large amounts may lead to the same side effects as those seen with large amounts of Vitamin A taken by mouth. Call the Poison Help line at 1-800-222-1222 if tretinoin gel (microsphere) is taken by mouth.

What should I avoid while using tretinoin gel (microsphere)?

- You should avoid sunlamps, tanning beds, and ultraviolet light during treatment with tretinoin gel (microsphere).
- Minimize exposure to sunlight.
- If you have to be in the sunlight, are sensitive to sunlight, or are using medicine that cause sensitive to sunlight, use a sunscreen with sun protection factor (SPF) of 15 or more. Wear a wide-brimmed hat or other protective clothing to cover the treated areas, even on days when it is not sunny, or you are inside.
- Do not use tretinoin gel (microsphere) on sunburn skin until your skin has healed.

What are the possible side effects of tretinoin gel (microsphere)?

Tretinoin gel (microsphere) can cause serious side effects, including:

- Skin irritation. Tretinoin gel (microsphere) can cause skin dryness, redness, swelling, peeling, itching, blistering, burning, or stinging. If you develop these symptoms, your healthcare provider may temporarily stop or completely stop your treatment with tretinoin gel (microsphere).

To help reduce the risk of skin irritation with tretinoin gel (microsphere):

- Avoid use of tretinoin gel (microsphere) in skin areas affected by eczema.
- Minimize or avoid use of tretinoin gel (microsphere) with weather extremes, such as severe wind or cold.
- Avoid washing the treated skin too often or scrubbing it hard when washing. Tretinoin gel (microsphere) is not recommended with use of medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high amounts of alcohol, astringents, spices, or lime peels.
- Apply a topical moisturizer when using tretinoin gel (microsphere). It is not known if tretinoin gel (microsphere) is effective when used less than 1 time a day.
 - **Sensitivity to sunlight.** See “**What should I avoid while using tretinoin gel (microsphere)?**”

The most common side effects of tretinoin gel (microsphere) include skin redness, pain, and itching.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of tretinoin gel (microsphere).

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

For more information, go to www.amneal.com or call 1-877-835-5472.

How should I store tretinoin gel (microsphere)?

- Store tretinoin gel (microsphere) at room temperature between 68° to 77°F (20° to 25°C).
- Store tretinoin gel (microsphere) pump upright.

Keep tretinoin gel (microsphere) and all medicines out of the reach of children.**General information about the safe and effective use of tretinoin gel (microsphere).**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use tretinoin gel (microsphere) for a condition for which it was not prescribed. Do not give tretinoin gel (microsphere) to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about tretinoin gel (microsphere) that is written for health professionals.

What are the ingredients of tretinoin gel (microsphere)?

Active ingredient: tretinoin, USP

Inactive ingredients: benzyl alcohol, butylated hydroxytoluene, carbomer 974P, cyclomethicone and PPG-18/18 dimethicone, disodium EDTA, glycerin, PPG-20 methyl glucose ether distearate, propylene glycol, purified water, sorbic acid, and trolamine, copolymer of methyl methacrylate and ethylene glycol dimethacrylate crosspolymer (microspheres system), propylene glycol dicaprylate/dicaprate

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

Rev. 04-2026-01

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

PRINCIPAL DISPLAY PANEL

NDC 69238-2323-1

Tretinoin Gel, USP (Microsphere)

0.08%

PUMP

For Topical Use Only

Rx only

**Net Wt.
50 g**

Amneal

Usual Dosage: See prescribing information.

WARNING: Keep out of the reach of children.

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

Store pump upright.

Each gram contains: Tretinoin, USP 0.08% in benzyl alcohol, butylated hydroxytoluene, carbomer 974P, cyclomethicone and PPG-18/18 dimethicone, disodium EDTA, glycerin, methyl methacrylate and ethylene glycol dimethacrylate crosspolymer (microspheres system), PPG-20 methyl glucose ether distearate, propylene glycol, propylene glycol dicaprylate/dicaprate, purified water, sorbic acid, and trolamine.

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 04-2026-01



3.5" x 0.75" Non-Varnish Area for
Lot No. and Exp. Date and Serialization

NDC 69238-2323-1

NDC 69238-2323-1

NDC 69238-2323-1

Usual Dosage: See prescribing information.

WARNING: Keep out of the reach of children.

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

Store pump upright.

Each gram contains: Tretinoin, USP 0.08% in benzyl alcohol, butylated hydroxytoluene, carbomer 974P, cyclomethicone and PPG-18/18 dimethicone, disodium EDTA, glycerin, methyl methacrylate and ethylene glycol dimethacrylate crosspolymer (microspheres system), PPG-20 methyl glucose ether distearate, propylene glycol, propylene glycol dicaprylate/dicaprate, purified water, sorbic acid, and trolamine.

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 04-2026-01



Tretinoin Gel, USP

(Microsphere)

0.08%

PUMP

For Topical Use Only

Tretinoin Gel, USP

(Microsphere)

0.08%

PUMP

For Topical Use Only

Tretinoin Gel, USP

(Microsphere)

0.08%

PUMP

For Topical Use Only

Net Wt.
50 g

Rx only

Net Wt.
50 g

Net Wt.
50 g

Amneal

Amneal

TRETINOIN

tretinoin gel

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:69238-2323
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TRETINOIN (UNII: 5688UTC01R) (TRETINOIN - UNII:5688UTC01R)	TRETINOIN	0.8 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
BENZYL ALCOHOL (UNII: LKG8494WBH)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
CARBOMER HOMOPOLYMER TYPE B (ALLYL PENTAERYTHRITOL CROSSLINKED) (UNII: HHT01ZNK31)	
CYCLOMETHICONE (UNII: NMQ347994Z)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	
GLYCERIN (UNII: PDC6A3C0OX)	
GLYCOL DIMETHACRYLATE (UNII: 7BK5G69305)	
METHYL METHACRYLATE (UNII: 196OC77688)	
PPG-20 METHYL GLUCOSE ETHER DISTEARATE (UNII: 0057334FAB)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
PROPYLENE GLYCOL DICAPRYLATE/DICAPRATE (UNII: O4446S9CRA)	
WATER (UNII: 059QF0KO0R)	
SORBIC ACID (UNII: X045WJ989B)	
TROLAMINE (UNII: 9O3K93S3TK)	

Product Characteristics

Color	white (white to very pale-yellow)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69238-2323-1	1 in 1 CARTON	05/15/2026	
1		50 g in 1 BOTTLE, PUMP; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA217497	05/15/2026	

Labeler - Amneal Pharmaceuticals NY LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals, LLC		079389286	analysis(69238-2323) , label(69238-2323) , manufacture(69238-2323) , pack(69238-2323)

