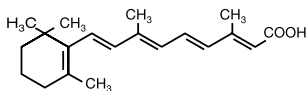


FOR TOPICAL USE ONLY. NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.

DESCRIPTION: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is a formulation containing 0.1% or 0.04%, by weight, tretinoin for topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (MICROSPONGE® System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel. Other components of this formulation are purified water, carbomer 974P (0.04% formulation), carbomer 934P (0.1% formulation), glycerin, disodium EDTA, propylene glycol, sorbic acid, PPG-20 methyl glucose ether distearate, cyclomethicone and dimethicone copolyol, benzyl alcohol, triethylamine, and butylated hydroxytoluene.

Chemically, tretinoin 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-non-tetraenoic acid. It is a member of the retinoid family of compounds, and a metabolite of naturally occurring Vitamin A. Tretinoin has a molecular weight of 300.44. Tretinoin has the following structure:



CLINICAL PHARMACOLOGY: Tretinoin is a retinoid metabolite of Vitamin A that binds to intracellular receptors in the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product.

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, other mechanisms, or both.

Mode of Action: Although the exact mode of action of tretinoin is unknown, current evidence suggests that the effectiveness of tretinoin in acne is due primarily to its ability to modify abnormal follicular keratinization. Comedones form in follicles with an excess of keratinized epithelial cells. Tretinoin promotes detachment of cornified cells and the enhanced shedding of corneocytes from the follicle. By increasing the mitotic activity of follicular epithelia, tretinoin also increases the turnover rate of thin, loosely-adherent corneocytes. Through these actions, the comedo contents are extruded and the formation of the microcomedo, the precursor lesion of acne vulgaris, is reduced.

Additionally, tretinoin acts by modulating the proliferation and differentiation of epidermal cells. These effects are mediated by tretinoin's interaction with a family of nuclear retinoic acid receptors. Activation of these nuclear receptors causes changes in gene expression. The exact mechanisms whereby tretinoin-induced changes in gene expression regulate skin function are not understood.

Pharmacokinetics: Tretinoin is a metabolite of Vitamin A metabolism in man. Percutaneous absorption, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in 44 healthy men and women. Estimates of *in vivo* bioavailability, mean (SD)%, following both single and multiple daily applications, for a period of 28 days with the 0.1% gel, were 0.82 (0.11)% and 1.41 (0.54)%, 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 Retin-A Micro (tretinoin gel) microsphere, 0.1%, relative to baseline levels. Clinical pharmacokinetic studies have not been performed with Retin-A Micro (tretinoin gel) microsphere, 0.04%.

INDICATIONS AND USAGE: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the use of this product in the treatment of other disorders have not been established.

CLINICAL STUDIES

Retin-A Micro (tretinoin gel) microsphere, 0.1%: In two vehicle-controlled studies, Retin-A Micro (tretinoin gel) microsphere, 0.1%, applied once daily was significantly more effective than vehicle in reducing the severity of acne lesion counts. The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in the following table:

Mean Percent Reduction in Lesion Counts Retin-A Micro (tretinoin gel) microsphere, 0.1%				
	Retin-A Micro (tretinoin gel) microsphere, 0.1%		Vehicle gel	
	Study #1 72 pts	Study #2 71 pts	Study #1 72 pts	Study #2 67 pts
Non-inflammatory lesion counts	49%	32%	22%	3%
Inflammatory lesion counts	37%	29%	18%	24%
Total lesion counts	45%	32%	23%	16%

Retin-A Micro (tretinoin gel) microsphere, 0.1%, was also significantly superior to the vehicle in the investigator's global evaluation of the clinical response. In Study #1, thirty-five percent (35%) of patients using Retin-A Micro (tretinoin gel) microsphere, 0.1%, achieved an excellent result, as compared to eleven percent (11%) of patients on the vehicle control. In Study #2, twenty-eight percent (28%) of patients using Retin-A Micro (tretinoin gel) microsphere, 0.1%, achieved an excellent result, as compared to nine percent (9%) of the patients on the vehicle control.

Retin-A Micro (tretinoin gel) microsphere, 0.04%: In two vehicle-controlled clinical studies, Retin-A Micro (tretinoin gel) microsphere, 0.04%, applied once daily was more effective ($p < 0.05$) than vehicle in reducing the acne lesion counts. The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in the following table:

Mean Percent Reduction in Lesion Counts Retin-A Micro (tretinoin gel) microsphere, 0.04%				
	Retin-A Micro (tretinoin gel) microsphere, 0.04%		Vehicle gel	
	Study #1 108 pts	Study #2 111 pts	Study #1 110 pts	Study #2 103 pts
Non-inflammatory lesion counts	37%	29%	-2%*	14%
Inflammatory lesion counts	44%	41%	13%	30%
Total lesion counts	40%	35%	8%	20%

* - That is, a mean percent increase of 2%

Retin-A Micro (tretinoin gel) microsphere, 0.04%, was also superior ($p < 0.05$) to the vehicle in the investigator's global evaluation of the clinical response. In study #1, fourteen percent (14%) of patients using Retin-A Micro (tretinoin gel) microsphere, 0.04%, achieved an excellent result compared to five percent (5%) of patients on vehicle control. In study #2, nineteen percent (19%) of patients using Retin-A Micro (tretinoin gel) microsphere, 0.04%, achieved an excellent result compared to nine percent (9%) of patients on vehicle control.

No studies were conducted comparing the efficacy of Retin-A Micro 0.04% to Retin-A Micro 0.1%. There is no evidence that Retin-A Micro 0.1% is more efficacious than Retin-A Micro 0.04% or that Retin-A Micro 0.04% is safer than Retin-A Micro 0.1%.

CONTRAINDICATIONS: This drug is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.

PRECAUTIONS:

General:

- The skin of certain individuals may become excessively dry, red, swollen, or blistered. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Excessive skin dryness may also be experienced; if so, use of an appropriate emollient during the day may be helpful.

- Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Use of sunscreen products (SPF 15) and protective clothing over treated areas are recommended when exposure cannot be avoided.

- Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

- Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, should be kept away from the eyes, the mouth, paranasal creases of the nose, and mucous membranes.

- Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

Information for Patients: See Patient Information leaflet.

Drug Interactions: Concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, or spices should be used with caution because of possible interaction with tretinoin. Avoid contact with the peel of limes. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%. It also is advisable to allow the effects of such preparations to subside before use of Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is begun.

Carcinogenesis, Mutagenesis, Impairment of Fertility: 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 these clinical formulations (0.04% and 0.1%). A dose-related 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 1.0 mg/kg/day, respectively. These doses are two and four times the maximum human systemic dose applied topically, when normalized for total body surface area. The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose (MTD) 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 maximum human systemic dose, normalized for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose applied topically is defined as 1 gram of Retin-A Micro (tretinoin gel) microsphere, 0.1% applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin gel) microsphere, 0.04% or 0.1%.

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.

The mutagenic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

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

In dermal Segment I fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (4 times the maximum human systemic dose applied topically, and normalized for total body surface area), and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day (2 times the maximum human systemic dose applied topically and normalized for total body surface area) and above were observed. In oral Segment I and Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (17 times the human topical dose normalized for total body surface area).

Dermal fertility and perinatal development studies with Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, have not been performed in any species.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

In a study of pregnant rats treated with topical application of Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.5 to 1 mg/kg/day on gestation days 6-15 (4 to 8 times the maximum human systemic dose of tretinoin normalized for total body surface area after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%) some alterations were seen in vertebrae and ribs of offspring. In another study, pregnant New Zealand white rabbits were treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at doses of 0.2, 0.5, and 1.0 mg/kg/day, administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. There appeared to be increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, 3 times the maximum human systemic dose of tretinoin after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area. In a repeat study of the highest topical dose (1.0 mg/kg/day) in pregnant rabbits, these effects were not seen, but a few alterations that may be associated with tretinoin exposure were seen. Other pregnant rabbits exposed topically for six hours to 0.5 or 1.0 mg/kg/day tretinoin while restrained in stocks to prevent ingestion, did not show any teratogenic effects at doses up to 17 times (1.0 mg/kg/day) the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, adjusted for total body

surface area, but fetal resorptions were increased at 0.5 mg/kg. In addition, topical tretinoin in non Retin-A Micro (tretinoin gel) microsphere formulations was not teratogenic in rats and rabbits when given in doses of 42 and 27 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively, (assuming a 50 kg adult applied a daily dose of 1.0 g of 0.1% gel topically). At these topical doses, however, delayed ossification of several bones occurred in rabbits. In rats, a dose-dependent increase of supernumerary ribs was observed.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. Tretinoin was teratogenic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). However, variations in teratogenic doses among various strains of rats have been reported. In the cynomolgus monkey, which metabolically is more similar to humans than other species in its handling of tretinoin, fetal malformations were reported for doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (83 times the maximum human systemic dose normalized for total body surface area), although increased skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in animal teratogenicity tests has generated equivocal results. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (8 times the maximum human systemic dose normalized for total body surface area). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

There are no adequate and well-controlled studies in pregnant women. Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of Retin-A. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Non-Teratogenic Effects: Topical tretinoin has been shown to be fetotoxic in rabbits when administered 0.5 mg/kg/day (8 times the maximum human systemic dose applied topically and normalized for total body surface area), resulting in fetal resorptions and variations in ossification. Oral tretinoin has been shown to be fetotoxic, resulting in skeletal variations and increased intrauterine death in rats when administered 2.5 mg/kg/day (21 times the maximum human systemic dose applied topically and normalized for total body surface area).

There are, however, no adequate and well-controlled studies in pregnant women.

Animal Toxicity Studies: In male mice treated topically with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at 0.5, 2.0, or 5.0 mg/kg/day tretinoin (2, 8, or 21 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area) for 90 days, a reduction in testicular weight, but with no pathological changes were observed at the two highest doses. Similarly, in female mice there was a reduction in ovarian weights, but without any underlying pathological changes, at 5.0 mg/kg/day (21 times the maximum human dose). In this study there was a dose-related increase in the plasma concentration of tretinoin 4 hours after the first dose. A separate toxicokinetic study in mice indicates that systemic exposure is greater after topical application to unrestrained animals than to restrained animals, suggesting that the systemic toxicity observed is probably related to ingestion. Male and female dogs treated with Retin-A Micro (tretinoin gel) microsphere, 0.1%, at 0.2, 0.5, or 1.0 mg/kg/day tretinoin (5, 12, or 25 times the maximum human systemic dose after topical administration of Retin-A Micro (tretinoin gel) microsphere, 0.1%, normalized for total body surface area, respectively) for 90 days showed no evidence of reduced testicular or ovarian weights or pathological changes.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A Micro (tretinoin gel) microsphere, 0.1% or 0.04%, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

Geriatric Use: Safety and effectiveness in a geriatric population have not been established. Clinical studies of Retin-A Micro did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS:

Irritation Potential:

Acne clinical trial results: In separate clinical trials for each concentration, acne patients treated with Retin-A Micro (tretinoin gel) microsphere 0.1% or 0.04%, analysis over the twelve week period showed that cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or itching peaked during the initial two weeks of therapy, decreasing thereafter.

Approximately half of the patients treated with Retin-A Micro 0.04% had cutaneous irritation at Week 2. Of those patients who did experience cutaneous side effects, 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 patients experienced moderate cutaneous irritation and there was no severe irritation at Week 2.

In studies on Retin-A Micro (tretinoin gel) microsphere, 0.04%, throughout the treatment period the majority of patients experienced some degree of irritation (mild, moderate, or severe) with 1% (2/225) of patients having scores indicative of a severe irritation rating; and 1.3% (3/225) of patients treated with Retin-A Micro (tretinoin gel) microsphere, 0.04%, discontinued treatment due to irritation, which included dryness in one patient and peeling and urticaria in another.

In studies on Retin-A Micro (tretinoin gel) microsphere, 0.1%, no more than 3% of patients had cutaneous irritation scores indicative of a severe irritation rating; although, 6% (14/224) of patients treated with Retin-A Micro (tretinoin gel) microsphere, 0.1% discontinued treatment due to irritation. Of these 14 patients, four had severe irritation after 3 to 5 days of treatment, with blistering in one patient.

Results in studies of subjects without acne: In a half-face comparison trial conducted for up to 14 days in women with sensitive skin, but without acne, Retin-A Micro (tretinoin gel) microsphere, 0.1% was statistically less irritating than tretinoin cream, 0.1%. In addition, a cumulative 21 day irritation evaluation in subjects with normal skin showed that Retin-A Micro (tretinoin gel) microsphere, 0.1%, had a lower irritation profile than tretinoin cream, 0.1%. The clinical significance of these irritation studies for patients with acne is not established. Comparable effectiveness of Retin-A Micro (tretinoin gel) microsphere, 0.1% and tretinoin cream, 0.1%, has not been established. The lower irritancy of Retin-A Micro (tretinoin gel) microsphere, 0.1% in subjects without acne may be attributable to the properties of its vehicle. The contribution to decreased irritancy by the MICROSPPONGE System has not been established. No irritation studies have been performed to compare Retin-A Micro (tretinoin gel) microsphere, 0.04%, with either Retin-A Micro (tretinoin gel) microsphere, 0.1%, or tretinoin cream, 0.1%.

The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. However, efficacy has not been established for lower dosing frequencies (see **DOSAGE AND ADMINISTRATION** Section).

True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin.

OVERDOSAGE: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, is intended for topical use only. If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, should be applied once a day, in the evening, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Application of excessive amounts of gel may result in "caking" of the gel, and will not provide incremental efficacy.

A transitory feeling of warmth or slight stinging may be noted on application. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or the frequency of application increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. Efficacy has not been established for less than once daily dosing frequencies.

During the early weeks of therapy, an apparent exacerbation of inflammatory lesions may occur. If tolerated, this should not be considered a reason to discontinue therapy.

Therapeutic results may be noticed after two weeks, but more than seven weeks of therapy are required before consistent beneficial effects are observed.

Patients treated with Retin-A Micro (tretinoin gel) microsphere, 0.1% and 0.04%, may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied.

HOW SUPPLIED:

Retin-A Micro® (tretinoin gel) microsphere, 0.1% is supplied as: 20g (NDC 0062-0190-02) and 45g (NDC 0062-0190-03) tubes.

Retin-A Micro® (tretinoin gel) microsphere, 0.04% is supplied as: 20g (NDC 0062-0204-02) and 45g (NDC 0062-0204-03) tubes.

Storage Conditions: Store at 15 °-25°C (59°-77°F).

Rx only.

Patent Nos.: 4,690,825; 5,145,675 & 5,955,109



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