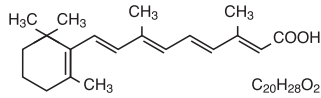


Prescribing Information

Description: TRETIN-X Gel, and Cream are used for the topical treatment of acne vulgaris. Each gram of TRETIN-X gel contains tretinoin in either of two strengths, 0.025% (0.25 mg) or 0.01% (0.1 mg) in a gel vehicle of hydroxypropyl cellulose, butylated hydroxytoluene, and alcohol (denatured with *tert*-butyl alcohol and brucine sulfate) 90% w/w. Each gram of TRETIN-X cream contains tretinoin in either of four strengths, 0.1% (1 mg), 0.05% (0.5 mg), 0.0375% (0.375 mg) or 0.025% (0.25 mg) in a hydrophilic cream vehicle of stearic acid, isopropyl myristate, polyoxyol 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water. Chemically, tretinoin is *all-trans*-retinoic acid. It has a molecular weight of 300.44 and has the following structural formula:



Clinical Pharmacology: Although the exact mode of action of TRETIN-X is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

Indications and Usage: TRETIN-X gel and cream are indicated for topical application in the treatment of acne vulgaris. The safety and efficacy of the long-term use of this product in the treatment of other disorders have not been established.

Contraindications: Use of the product should be discontinued if hypersensitivity to any of the ingredients is noted.

Warnings: GELS ARE FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING USE. Keep out of reach of children. Keep tube tightly closed. Do not expose to heat or store at temperatures above 120°F (49°C).

Precautions: General: If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of TRETIN-X, 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 and protective clothing over treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

TRETIN-X preparations for acne treatment should be kept away from the eyes, the mouth, angles of the nose, and mucous membranes. Topical use may induce severe local erythema and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, discontinue use temporarily, or discontinue use altogether. Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

Drug Interactions: Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution because of possible interaction with tretinoin. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid with TRETIN-X. It also is advisable to "rest" a patient's skin until the effects of such preparations subside before use of TRETIN-X is begun.

Carcinogenesis, Mutagenesis, Impairment to 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. 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, when adjusted 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, adjusted for total body surface area). For purposes of comparisons of the animal exposure to systemic human exposure, the maximum human systemic dose is defined as 1 gram of 0.1% TRETIN-X applied daily to a 50 kg person (0.02 mg tretinoin/kg body weight).

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.

In dermal Segment I fertility studies of tretinoin 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 adjusted 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 adjusted for total body surface area) and above were observed. A dermal Segment III study with TRETIN-X has not been performed in any species. 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 (16 times the human topical dose adjusted for total body surface area).

Pregnancy: Teratogenic effects. Pregnancy Category C. Oral tretinoin has been shown to be teratogenic in rats, mice, hamsters, and subhuman primates. It was teratogenic and fetotoxic in Wistar rats when given orally or topically in doses greater than 1 mg/kg/day (8 times the maximum human systemic dose adjusted 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 closer to humans for tretinoin than the other

species examined, fetal malformations were reported at doses of 10 mg/kg/day or greater, but none were observed at 5 mg/kg/day (83 times the maximum human systemic dose adjusted for total body surface area), although increased skeletal variations were observed at all doses. A dose-related increase in embryoletality and abortion was 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 adjusted 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.

There are other reports in New Zealand White rabbits administered doses of greater than 0.2 mg/kg/day (3.3 times the maximum human systemic dose adjusted for total body surface area) of an increased incidence of domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species.

In contrast, several well-controlled animal studies have shown that dermally applied tretinoin may be fetotoxic, but not overly teratogenic in rats and rabbits at doses of 1.0 and 0.5 mg/kg/day, respectively (8 times the maximum human systemic dose adjusted for total body surface area in both species).

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 tretinoin. 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.

Nonteratogenic 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 adjusted for total body surface area). 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 (20 times the maximum human systemic dose adjusted for total body surface area). There are no adequate and well-controlled studies in pregnant women. Tretinoin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 TRETIN-X is used by a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients 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 tretinoin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients.

Adverse Reactions: 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. True contact allergy to topical tretinoin is rarely encountered. Temporary hyper- or hypopigmentation has been reported with repeated application of a tretinoin preparation. Some individuals have been reported to have heightened susceptibility to sunlight while under treatment with tretinoin. To date, all adverse effects of tretinoin have been reversible upon discontinuance of therapy (**see Dosage and Administration Section**).

Overdosage: 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 the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

Dosage and Administration: TRETIN-X gel or cream should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. Gel: Excessive application results in "pilling" of the gel, which minimizes the likelihood of over-application by the patient.

Application may cause a transitory feeling of warmth or slight stinging. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or frequency of application increased when the patients become able to tolerate the treatment.

Alterations of vehicle, drug concentration, or dose frequency should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance.

During the early weeks of therapy, an *apparent* exacerbation of inflammatory lesions may occur. This is due to the action of the medication on deep, previously unseen lesions and should not be considered a reason to discontinue therapy.

Therapeutic results should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen.

Once the acne lesions have responded satisfactorily, it may be possible to maintain the improvement with less frequent applications, or other dosage forms.

Patients treated with TRETIN-X preparations may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied (**see Precautions**).

How Supplied:

TRETIN-X Gel			TRETIN-X Cream		
NDC CODE	Strength	Qty.	NDC CODE	Strength	Qty.
14290-378-35	0.025%	35 g	14290-375-35	0.1%	35 g
14290-379-35	0.01%	35 g	14290-381-35	0.0375%	35 g
			14290-377-35	0.05%	35 g
			14290-376-35	0.025%	35 g

Storage Conditions:

TRETIN-X Gel: store below 30°C (86°F). TRETIN-X Cream: store below 27°C (80°F)

TRETIN-X is a registered trademark of Triax Pharmaceuticals, LLC.

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