

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 75265**

**PRINTED LABELING**

75-265



DEC 24 1998

P480500

# Tretinoin Cream, USP

8026

## PATIENT INSTRUCTIONS

# Acne Treatment

### IMPORTANT

Read Directions Carefully Before Using

**Rx only**

**For External Use Only. Not For Ophthalmic Use.**

**THIS LEAFLET TELLS YOU ABOUT TRETINOIN ACNE TREATMENT AS PRESCRIBED BY YOUR PHYSICIAN. THIS PRODUCT IS TO BE USED ONLY ACCORDING TO YOUR DOCTOR'S INSTRUCTIONS, AND IT SHOULD NOT BE APPLIED TO OTHER AREAS OF THE BODY OR TO OTHER GROWTHS OR LESIONS. THE LONG-TERM SAFETY AND EFFECTIVENESS OF THIS PRODUCT IN OTHER DISORDERS HAVE NOT BEEN EVALUATED. IF YOU HAVE ANY QUESTIONS, BE SURE TO ASK YOUR DOCTOR.**

#### WARNINGS AND PRECAUTIONS

**The effects of the sun on your skin.** As you know, overexposure to natural sunlight or the artificial sunlight of a sunlamp can cause sunburn. Overexposure to the sun over many years may cause premature aging of the skin and even skin cancer. The chances of these effects occurring will vary depending on skin type, the climate and the care taken to avoid overexposure to the sun. Therapy with tretinoin may make your skin more susceptible to sunburn and other adverse effects of the sun, so unprotected exposure to natural or artificial sunlight should be minimized.

**Laboratory findings.** When laboratory mice are exposed to artificial sunlight, they often develop skin tumors. These sunlight-induced tumors may appear more quickly and in greater number if the mouse is also topically treated with the active ingredient tretinoin. In some studies, under different conditions, however, when mice treated with tretinoin were exposed to artificial sunlight, the incidence and rate of development of skin tumors was reduced. There is no evidence to date that tretinoin alone will cause the development of skin tumors in either laboratory animals or humans. However, investigations in this area are continuing.

**Use caution in the sun.** When outside, even on hazy days, areas treated with tretinoin should be protected. An effective sunscreen should be used any time you are outside (consult your physician for a recommendation of an SPF level which will provide you with the necessary high level of protection). For extended sun exposure, protective clothing, like a hat, should be worn. Do not use artificial sunlamps while you are using tretinoin. If you do become sunburned, stop your therapy with tretinoin until your skin has recovered.

**Avoid excessive exposure to wind or cold.** Extremes of climate tend to dry or burn normal skin. Skin treated with tretinoin may be more vulnerable to these extremes. Your physician can

recommend ways to manage your acne treatment under such conditions.

**Possible problems.** The skin of certain sensitive individuals may become excessively red, swollen, blistered or crusted. If you are experiencing severe or persistent irritation, discontinue the use of tretinoin and consult your physician.

There have been reports that, in some patients, areas treated with tretinoin developed a temporary increase or decrease in the amount of skin pigment (color) present. The pigment in these areas returned to normal either when the skin was allowed to adjust to tretinoin or therapy was discontinued.

**Use other medication only on your physician's advice.** Only your physician knows which other medications may be helpful during treatment and will recommend them to you if necessary. Follow the physician's instructions carefully. In addition, you should avoid preparations that may dry or irritate your skin. These preparations may include certain astringents, toiletries containing alcohol, spices or lime, or certain medicated soaps, shampoos and hair permanent solutions. Do not allow anyone else to use this medication.

Do not use other medications with tretinoin which are not recommended by your doctor. The medications you have used in the past might cause unnecessary redness or peeling.

**If you are pregnant, think you are pregnant or are nursing an infant:** No studies have been conducted in humans to establish the safety of tretinoin in pregnant women. If you are pregnant, think you are pregnant, or are nursing a baby, consult your physician before using this medication.

#### AND WHILE YOU'RE ON TRETINOIN THERAPY

**Use a mild, non-medicated soap.** Avoid frequent washings and harsh scrubbing. Acne isn't caused by dirt, so no matter how hard you scrub, you can't wash it away. Washing too frequently or scrubbing too roughly may at times actually make your acne worse. Wash your skin gently with a mild, bland soap. Two or three times a day should be sufficient. Pat skin dry with a towel. Let the face dry 20 to 30 minutes before applying tretinoin. Remember, excessive irritation such as rubbing, too much washing, use of other medications not suggested by your physician, etc., may worsen your acne.

Remove this portion before dispensing.

**Tretinoin 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 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 tretinoin. It also is advisable to "rest" a patient's skin until the effects of such preparations subside before use of tretinoin is begun.

**Carcinogenesis:** Long-term animal studies to determine the carcinogenic potential of tretinoin have not been performed. Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of weakly carcinogenic light from a solar simulator. In other studies, when lightly pigmented hairless mice treated with tretinoin were exposed to carcinogenic doses of UVB light, the incidence and rate of development of skin tumors was reduced. Due to significantly different experimental conditions, no strict comparison of these disparate data is possible. Although the significance of these studies to man is not clear, patients should avoid or minimize exposure to sun.

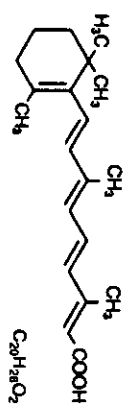
**Pregnancy:** Teratogenic effects: Pregnancy Category C. Oral tretinoin has been shown to be teratogenic in rats when given in doses 1000 times the topical human dose. Oral tretinoin has been shown to be fetotoxic in rats when given in doses 500 times the topical human dose.

**Clinical Pharmacology:** Although the exact mode of action of tretinoin 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:** Tretinoin cream is 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.

**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 tretinoin, 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.



**Description:** Tretinoin Cream, USP is used for the topical treatment of acne vulgaris. Each gram of tretinoin cream contains tretinoin 0.05% (0.5 mg) in a hydrophilic cream vehicle which includes the following inactive ingredients: butylated hydroxytoluene, isopropyl myristate, polyoxy 40 stearate, purified water, sorbic acid, stearic acid, stearyl alcohol, and xanthan gum. Chemically, tretinoin is all-trans-retinoic acid. It has a molecular weight of 300.44 and the following structural formula:

# Tretinoin Cream, USP

8029

**For External Use Only. Not For Ophthalmic Use.**

**Rx only**

75-265

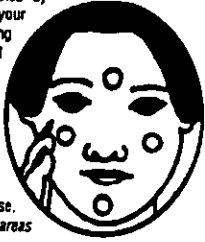
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HOW TO USE TRETINOIN

To get the best results with tretinoin therapy, it is necessary to use it properly. Forget about the instructions given for other products and the advice of friends. Just stick to the special plan your doctor has laid out for you and be patient. Remember, when tretinoin is used properly, many users see improvement by 12 weeks. AGAIN, FOLLOW INSTRUCTIONS — BE PATIENT — DON'T START AND STOP THERAPY ON YOUR OWN — IF YOU HAVE QUESTIONS, ASK YOUR DOCTOR.

To help you use the medication correctly, keep these simple instructions in mind.

- Apply tretinoin once daily before bedtime, or as directed by your physician. Your physician may advise, especially if your skin is sensitive, that you start your therapy by applying tretinoin every other night. First, wash with a mild soap and dry your skin gently. WAIT 20 TO 30 MINUTES BEFORE APPLYING MEDICATION; it is important for skin to be completely dry in order to minimize possible irritation.
- It is better not to use more than the amount suggested by your physician or to apply more frequently than instructed. Too much may irritate the skin, waste medication and won't give faster or better results.
- Keep the medication away from the corners of the nose, mouth, eyes and open wounds. Spread away from these areas when applying.
- Cream: Squeeze about a half inch or less of medication onto the fingertip. While that should be enough for your whole face, after you have some experience with the medication you may find you need slightly more or less to do the job. The medication should become invisible almost immediately. If it is still visible, you are using too much. Cover the affected area lightly with tretinoin cream by first dabbing it on your forehead, chin and both cheeks, then spreading it over the entire affected area. Smooth gently into the skin.
- It is recommended that you apply a moisturizer or a moisturizer with sunscreen that will not aggravate your acne (noncomedogenic) every morning after you wash.



WHAT TO EXPECT WITH YOUR NEW TREATMENT

Tretinoin works deep inside your skin and this takes time. You cannot make tretinoin work any faster by applying more than one dose each day, but an excess amount of tretinoin may irritate your skin. Be patient.

Remove this portion before dispensing.

Topical tretinoin has not been shown to be teratogenic in rats and rabbits when given in doses of 100 and 320 times the topical human dose, respectively (assuming a 50 kg adult applies 250 mg of 0.1% cream topically). However, at these topical doses, delayed ossification of a number of bones occurred in both species. These changes may be considered variants of normal development and are usually corrected after weaning. 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 tretinoin is used by a nursing woman.

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: Tretinoin 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. 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 tretinoin preparations may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied. (See Precautions)

How Supplied: Tretinoin Cream, USP is supplied as:

NDC CODE	Strength/Form	Qty
0781-7047-22	0.05% Cream	20 g
0781-7047-19	0.05% Cream	45 g

Storage Conditions: Store below 27°C (80°F). Rev. 98-4 8029

C98/4

Distributed By Geneva Pharmaceuticals, Inc. Broomfield, CO 80020



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LM971072

NDC 0781-7047-19

# Tretinoin Cream, USP

0.05%

NET WT. 45 g  
Rx only

Dist. By **Geneva** Pharmaceuticals, Inc.  
Brooklyn, NY 11201  
CO 80020

**For External Use Only. Not for Ophthalmic Use.**  
Each gram contains tretinoin 0.05% (0.5 mg) in a hydrophilic cream vehicle which includes the following inactive ingredients: stearic acid, isopropyl myristate, polyoxyl 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water.  
Usual Dosage: See package insert.  
Store below 27°C (80°F).  
Warning: **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

Pharmacist please note the combined insert: Unless otherwise instructed by physician, dispense prescription with patient package insert only. Remove physician package insert at perforation.

Rev. 98-3M

C98/4

P102630

NDC 0781-7047-19

# Tretinoin Cream, USP

0.05%

NET WT. 45 g  
Rx only

Dist. By **Geneva** Pharmaceuticals, Inc.  
Brooklyn, NY 11201  
CO 80020

**Important:** The opening of this product is covered by a metal seal. If this seal has been punctured or is not visible, do not use and return product 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.

See end flap for lot number and expiration date.



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TOP

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O.B.187.5 X 128  
LM971071  
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TOP

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LM971071

NDC 0781-7047-22

**Tretinoin Cream, USP**  
0.05%

NET WT. 20g  
g only

**Genevo**  
Pharmaceuticals, Inc.

**For External Use Only. Not for Ophthalmic Use.**  
Each gram of this cream contains 0.05 mg (0.5 mg) in a hydrophilic cream vehicle which includes the following inactive ingredients: stearic acid, sorbic acid, polyoxyethylene 40 stearate, stearyl alcohol, xanthan gum, sodium lauryl sulfate, sodium hydroxide, and purified water.  
Usual Dosage: See package insert.  
Store below 27°C (80°F).  
Warning: **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

Pharmacist please note the combined insert. Unless otherwise instructed by physician, dispense prescription with patient package insert only. Remove physician package insert at perforation.  
Rev. 98-3M  
C98/4

NDC 0781-7047-22

**Tretinoin Cream, USP**  
0.05%

NET WT. 20g  
g only

**Genevo**  
Pharmaceuticals, Inc.

Important: The opening of this product is covered by a metal seal. If this seal has been punctured or is not visible, do not use and return product 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.

See end flap for lot number and expiration date.



N 0781-7047-22 9

P102620

**Tretinoin Cream, USP**  
0.05%

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SIDE



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CAP END SHOULDER  
FREE COPY AREA

DEC 24 1998

\* FREE COPY AREA, FREE COPY AREA FOR CRIMP,  
EYEMARK LOCATION AND BARE METAL:  
MOST CRIMPING VALVES SUPPLIED,  
PLEASE CHECK WITH YOUR FILLING EQUIPMENT

5 3/8"  
TUBE  
LENGTH

FREE COPY AREA FOR CRIMP

EYEMARK LOCATION  
BARE METAL

OPEN END


**Tretinoin Cream, USP**  
 0.05%  
 NET WT 4.5 g (0.158 oz)  
 (0.9000)

NDC 0781-7047-19

Made in the USA  
 Distributed by  
**Geneva** Biocombustibles  
 14400 E. 2nd Ave. Denver, CO 80231

Each gram contains tretinoin 0.05% (0.5 mg) in a hydrophilic cream vehicle which includes the following inactive ingredients: stearic acid, isopropyl myristate, polyoxy 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water.

**For External Use Only. Not for Ophthalmic Use.**

Usual Dosage: See package insert.

Store below 27°C (80°F).

**Important:** Do not use if seal has been punctured or is not visible.

**To Open:** Use cap to puncture seal.

**Warning: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

See crimp end for lot number and expiration date.

Rev. 98-3M P850540 C98/4



75" 265"

CAP END  
FREE COPY AREA  
ENCLOSURE

DEC 24 1998

3 7/8"  
TUBE  
LENGTH

\* FREE COPY AREA, FREE COPY AREA FOR COMPANY,  
EXTERNAL LOCATION AND BARE METAL.


MOST COMMON VALVES SUPPLIER  
PLEASE CHECK WITH YOUR FILLING EQUIPMENT

FREE COPY AREA OF CRIMP

EYE MARK LOCATION  
BARE METAL

OPEN END

NDC 0781-7047-22

 **Tretinoin Cream, USP**  
**0.05%**  
 NET WT. 20g  
 For External Use Only

Made By **Geneva** (Parsippany, NJ)  
A Division of **Geneva Pharmaceuticals, Inc.** (CO 80020)

Each gram contains tretinoin 0.05% (0.5 mg) in a hydrophilic cream vehicle which includes the following inactive ingredients: stearic acid, isopropyl myristate, polyoxyl 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water.  
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 Store below 27°C (80°F).  
 Important: Do not use if seal has been punctured or is not visible.  
 To Open: Use cap to puncture seal.  
 Warning: KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.  
 See crimp end for lot number and expiration date.  
 Rev 96-3M P850520 C984



077  
120