CENTER FOR DRUG EVALUATION AND RESEARCH

75-260

APPLICATION NUMBER:

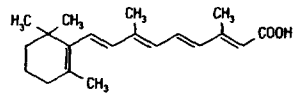
APPROVED DRAFT LABELING

TRETINOIN TOPICAL SOLUTION, USP 0.05%

For Topical Use Only

DESCRIPTION

Tretinoin topical solution is used for the topical treatment of acne vulgaris. It contains tretinoin 0.05% by weight, Polyethylene Glycol 400, NF; Butylated Hydroxytoluene and Alcohol 55% (v/v). Chemically, tretinoin is *all-trans*-retinoic acid and has the following structure:



$C_{20}H_{28}O_2$ M. W. 300.44

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 topical solution 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 this product, 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.

Tretinoin preparation 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 this product. It also is advisable to "rest" a patient's skin until the effects of such preparations subside before use of this product 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.

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 this product is administered to 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 this product. 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**).

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 topical solution, 0.05% should be applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly. It may be applied using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the liquid would run into areas where treatment is not intended.

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 preparation for acne may use cosmetics, but the areas to be treated should be cleansed thoroughly before the medication is applied. (See **PRECAUTIONS**).

HOW SUPPLIED

Tretinoin Topical Solution, USP 0.05% is a clear, yellow liquid supplied in 28 mL bottles.

Store below 30 °C (86 °F).

Rx Only

Prod. No.: 8151

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

28151
ISS. 5-98

TRETINOIN TOPICAL SOLUTION, USP 0.05%

PATIENT INSTRUCTIONS
Acne Treatment
IMPORTANT

Read Directions Carefully Before Using

JAN 25 199

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 this product 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 in this product, 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 this product 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 this product. If you do become sunburned, stop your therapy with this product 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 this product 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 this product and consult your physician.
There have been reports that, in some patients, areas treated with this product 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 this product 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 this product 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 this product 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 this product. Remember, excessive irritation such as rubbing, too much washing, use of other medications not suggested by your physician, etc., may worsen your acne.

HOW TO USE THIS PRODUCT

To get the best results with this 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 this product 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 this product 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 this product 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.*
- It may be applied to the skin where acne lesions appear, spreading the medication over the entire affected area, using a fingertip, gauze pad, or cotton swab. If gauze or cotton is employed, care should be taken not to oversaturate it to the extent that the liquid would run into areas where treatment is not intended (such as corners of the mouth, eyes, and nose).
- 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

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

There may be some discomfort or peeling during the early days of treatment. Some patients also notice that their skin begins to take on a blush.

These reactions do not happen to everyone. If they do, it is just your skin adjusting to this product and this usually subsides within two to four weeks. These reactions can usually be minimized by following instructions carefully. Should the effects become excessively troublesome, consult your doctor.

BY THREE TO SIX WEEKS, some patients notice an appearance of new blemishes (papules and pustules). At this stage it is *important to continue* using this product.

If this product is going to have a beneficial effect for you, you should notice a continued improvement in your appearance after 6 to 12 weeks of therapy. Don't be discouraged if you see no immediate improvement. Don't stop treatment at the first signs of improvement.

Once your acne is under control you should continue regular application of this product until your physician instructs otherwise.

IF YOU HAVE QUESTIONS

All questions of a medical nature should be taken up with your doctor.

Prod. No.: 8151

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

28151A
ISS. 5-98

MGP

NDC 60432-151-30

TRETINOIN TOPICAL SOLUTION, USP

0.05%

For Topical Use Only

Contains tretinoin 0.05% by weight, Polyethylene Glycol 400, NF; Butylated Hydroxytoluene, and Alcohol 55%.

SAFETY SEALED BOTTLE

Rx Only

NET: 28 mL

Manufactured By:
Morton Grove
Pharmaceuticals, Inc.
Morton Grove, IL 60053

BOXALL, INC.

3 60432-151-30 6

NET: 28 mL

TRETINOIN TOPICAL SOLUTION, USP 0.05%

NDC 60432-151-30

USUAL DOSAGE: Apply as directed by physician (see package insert).

WARNING: KEEP OUT OF THE REACH OF CHILDREN.

Store below 30 °C (86 °F).

Pharmacist: Unless otherwise instructed by physician, dispense prescription with package insert only.

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

5-50-8151-30
ISS. 5-98