RENOVA®

(TRETINOIN EMOLLIENT CREAM)

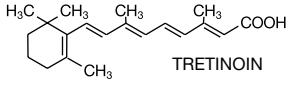
0.05%

FOR TOPICAL USE ON THE FACE ONLY

Prescribing Information

DESCRIPTION:

RENOVA (tretinoin emollient cream) 0.05% contains the active ingredient tretinoin (a retinoid) in an emollient cream base. Tretinoin is a yellow to light orange crystalline powder having a characteristic floral odor. Tretinoin is soluble in dimethylsulfoxide, slightly soluble in polyethylene glycol 400, octanol, and 100% ethanol. It is practically insoluble in water and mineral oil, and it is insoluble in glycerin. The chemical name for tretinoin is (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclonexen-1-yl)-2,4,6,8-nonatetraenoic acid. Tretinoin is also referred to as all-*trans*-retinoic acid and has a molecular weight of 300.44. The structural formula is represented below.



TRETINOIN

Tretinoin is available as RENOVA at a concentration of 0.05% w/w in a water in oil emulsion formulation consisting of light mineral oil, NF; sorbitol solution, USP; hydroxyoctacosanyl hydroxystearate; methoxy PEG-22/dodecyl glycol copolymer; PEG-45/dodecyl glycol copolymer; stearoxytrimethylsilane and stearyl alcohol; dimethicone 50 cs; methylparaben, NF; edetate disodium, USP; quaternium-15; butylated hydroxytoluene, NF; citric acid monohydrate, USP; fragrance; and purified water, USP.

CLINICAL PHARMACOLOGY:

The exact mechanism of action of tretinoin is unknown although retinoids are believed to exert an effect on the growth and differentiation of various epithelial cells. When applied topically, however, there was no noted increase in desmosine, hydroxyproline, or elastin mRNA in human skin. In addition, the role of the irritative nature of this product in effecting the positive effects attributed to this product for its indication has not yet been fully determined.

The transdermal absorption of tretinoin from various topical formulations ranged from 1% to 31% of applied dose, depending on whether it was applied to healthy skin or dermatitic skin. When percutaneous absorption of RENOVA was assessed in healthy male subjects (n=14) after a single application, as well as after repeated daily applications for 28 days, the absorption of tretinoin was less than 2% and endogenous concentrations of tretinoin and its major metabolites were unaltered.

INDICATIONS AND USAGE:

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)

RENOVA (tretinoin emollient cream) 0.05% is indicated as an adjunctive agent (see second bullet point below) for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin in patients who do not achieve such palliation using comprehensive skin care and sun avoidance programs alone (see bullet point 3 for populations in which effectiveness has not been established). **RENOVA DOES NOT ELIMINATE WRINKLES, REPAIR SUN DAMAGED SKIN, REVERSE PHOTO-AGING, or RESTORE A MORE YOUTHFUL or YOUNGER DERMAL HISTOLOGIC PATTERN.** Many patients achieve desired palliative effects on fine wrinkling, mottled hyperpigmentation, and tactile roughness of facial skin with the use of comprehensive skin care and sun avoidance programs including sunscreens, protective clothing, and emollient creams **NOT** containing tretinoin.

- RENOVA has demonstrated NO MITIGATING EFFECT on significant signs of chronic sun exposure such as coarse or deep wrinkling, skin yellowing, lentigines, telangiectasia, skin laxity, keratinocytic atypia, melanocytic atypia, or dermal elastosis.
- RENOVA should only be used under medical supervision as an adjunct to a comprehensive skin care and sun avoidance program that includes the use of effective sunscreens (minimum SPF of 15) and protective clothing when desired results on fine wrinkles, mottled hyperpigmentation, and roughness of facial skin have not been achieved with a comprehensive skin care and sun avoidance program alone.
- The effectiveness of RENOVA in the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin has not been established in people greater than 50 years of age OR in people with moderately to heavily pigmented skin. In addition, patients with visible actinic keratoses and patients with a history of skin cancer were excluded from clinical trials of RENOVA. Thus the effectiveness and safety of RENOVA in these populations are not known at this time.
- Neither the safety nor the effectiveness of RENOVA for the prevention or treatment of actinic keratoses or skin neoplasms has been established.
- Neither the safety nor the efficacy of using RENOVA daily for greater than 48 weeks has been established, and daily use beyond 48 weeks has not been systematically and histologically investigated in adequate and well-controlled trials. (See **WARNINGS** section.)

CLINICAL TRIALS DATA:

Two adequate and well-controlled trials were conducted involving a total of 161 evaluable patients (under 50 years of age) treated with RENOVA and 154 evaluable patients treated with the vehicle emollient cream on the face for 24 weeks as an adjunct to a comprehensive skin care and sun avoidance program, to assess the effects on fine wrinkling, mottled hyperpigmentation, and tactile skin roughness. Patients were evaluated at baseline on a 10 point scale and changes from that baseline rating were categorized as follows:

No Improvement: No change or an increase of 1 unit or more.

Minimal Improvement: Reduction of 1 unit.

Moderate Improvement: Reduction of 2 units or more.

In these trials, the fine wrinkles, mottled hyperpigmentation, and tactile roughness of the facial skin were thought to be caused by multiple factors which included intrinsic aging or environmental factors, such as chronic sun exposure.

The results of these assessments are as follows:

FINE WRINKLING			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA +CSP*	36%	40%	24%
Vehicle + CSP	62%	30%	8%

MOTTLED HYPERPIGMENTATION			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA +CSP	35%	27%	38%
Vehicle + CSP	53%	21%	27%

TACTILE SKIN ROUGHNESS			
	NO IMPROVEMENT	MINIMAL IMPROVEMENT	MODERATE IMPROVEMENT
RENOVA +CSP	49%	35%	16%
Vehicle + CSP	67%	23%	10%

*CSP = Comprehensive skin protection and sun avoidance programs including use of sunscreens, protective clothing, and emollient cream.

Most of the improvement in these signs was noted during the first 24 weeks of therapy. Thereafter, therapy primarily maintained the improvement realized during the first 24 weeks.

A majority of patients will lose most mitigating effects of RENOVA on fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin with discontinuation of a comprehensive skin care and sun avoidance program including RENOVA; however, the safety and effectiveness of using RENOVA daily for greater than 48 weeks have not been established.

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.

WARNINGS:

- RENOVA is a dermal irritant, and the results of continued irritation of the skin for greater than 48 weeks in chronic, long term use are not known. There is evidence of atypical changes in melanocytes and keratinocytes, and of increased dermal elastosis in some patients treated with RENOVA for longer than 48 weeks. The significance of these findings is unknown.
- Safety and effectiveness of RENOVA in individuals with moderately or heavily pigmented skin have not been established.
- RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided or minimized during use of RENOVA. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using RENOVA. Patients with sunburn should be advised not to use RENOVA until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using RENOVA and assure that the precautions outlined in the Patient Package Insert are observed.

RENOVA should be kept out of the eyes, mouth, angles of the nose, and mucous membranes. Topical use may cause severe local erythema, pruritus, burning, stinging, and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use less medication, decrease the frequency of application, discontinue use temporarily, or discontinue use altogether.

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

Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

PRECAUTIONS:

General: RENOVA should only be used as an adjunct to a comprehensive skin care and sun avoidance program. (See **INDICATIONS AND USAGE** section.)

If a drug sensitivity, chemical irritation, or a systemic adverse reaction develops, use of RENOVA should be discontinued.

Weather extremes, such as wind or cold, may be more irritating to patients using RENOVA.

Information for Patients: See Patient Package Insert.

Drug Interactions: Concomitant topical medications, medicated or abrasive soaps, shampoos, cleansers, cosmetics with a strong drying effect, products with high concentrations of alcohol, astringents, spices or lime, permanent wave solutions, electrolysis, hair depilatories or waxes, and products that may irritate the skin should be used with caution in patients being treated with RENOVA because they may increase irritation with RENOVA.

RENOVA should not be administered if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a life-time dermal study in CD-1 mice, at 100 and 200 times the average recommended human topical clinical dose, a few skin tumors in the female mice and liver tumors in male mice were observed. 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 tretinoin was administered topically at a dose 5 times the average recommended human topical clinical dose. For purposes of comparisons of the animal exposure to human exposure, the "recommended human topical clinical dose" is defined as 500 mg of 0.05% RENOVA applied daily to a 50 kg person.

In a chronic, two-year bioassay of Vitamin A acid in mice performed by Tsubura and Yamamoto, generalized amyloid deposition was reported in all groups in the basal layer of the Vitamin A treated skin. In CD-1 mice, a similar study reported hyalinization at the treated skin sites and the incidence of this finding was 0/50, 3/50, 3/50, and 2/50 in male mice and 1/50, 0/50, 4/50, and 2/50 in female mice from the vehicle control, 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg groups, respectively.

Studies in hairless albino mice suggest that tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA 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 were either reduced or

no effect was seen. Due to significantly different experimental conditions, no strict comparison of these disparate data is possible at this time. Although the significance of these studies to humans is not clear, patients should minimize exposure to sun.

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

Dermal Segment I and III studies with RENOVA have 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 (>400 times the average recommended human topical clinical dose).

Pregnancy:

Teratogenic effects: Pregnancy Category C.

ORAL tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and subhuman primates. It was teratogenic and fetotoxic in rats when given orally in doses 1000 times the average recommended human topical clinical dose. 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 (1000 times the average recommended human topical clinical dose), although increased skeletal variations were observed at all doses. A dose-related increased embryolethality 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 (200 times the recommended human topical clinical dose). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was dermally applied.

There are other reports in New Zealand White rabbits with doses of approximately 80 times the recommended human topical clinical dose 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 was not teratogenic at doses of 100 and 200 times the recommended human topical clinical dose, in rats and rabbits, respectively.

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 cases of temporally-associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin (Retin-A). Although no definite pattern of teratogenicity and no causal association has been established from these cases, 5 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:

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 100 times the recommended topical human clinical dose. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 500 times the recommended topical human clinical dose.

There are, however, no adequate and well-controlled studies in pregnant women. RENOVA should not be used during pregnancy.

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 RENOVA is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in patients less than 18 years of age have not been established.

Geriatric Use: Safety and effectiveness in individuals older than 50 years of age have not been established.

ADVERSE REACTIONS:

(See **WARNINGS** and **PRECAUTIONS** sections.)

In double-blind, vehicle-controlled studies involving 179 patients who applied RENOVA to their face, adverse reactions associated with the use of RENOVA were limited primarily to the skin. During these trials, 4% of patients had to discontinue use of RENOVA because of adverse reactions. These discontinuations were due to skin irritation or related cutaneous adverse reactions.

Local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus were reported by almost all subjects during therapy with RENOVA. These signs and symptoms were usually of mild to moderate severity and generally occurred early in therapy. In most patients the dryness, peeling, and redness recurred after an initial (24 week) decline.

OVERDOSAGE:

Application of larger amounts of medication than recommended will not lead to more rapid or better results, 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:

- Do NOT use RENOVA if the patient is pregnant or is attempting to become pregnant or is at high risk of pregnancy,
- Do NOT use RENOVA if the patient is sunburned or if the patient has eczema or other chronic skin condition(s),
- Do NOT use RENOVA if the patient is inherently sensitive to sunlight,
- Do NOT use RENOVA if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the possibility of augmented phototoxicity.

Patients require detailed instruction to obtain maximal benefits and to understand all the precautions necessary to use this product with greatest safety. The physician should review the Patient Package Insert.

RENOVA should be applied to the face once a day before retiring using only enough to cover the entire affected area lightly. Patients should gently wash their face with a mild soap, pat the skin dry, and wait 20 to 30 minutes before applying RENOVA. The patient should apply a pea-sized amount of cream to cover the entire face lightly. Special caution should be taken when applying the cream to avoid the eyes, ears, nostrils, and mouth.

Application of RENOVA may cause a transitory feeling of warmth or slight stinging.

Mitigation (palliation) of facial fine wrinkling, mottled hyperpigmentation and tactile roughness may occur gradually over the course of therapy. Up to six months of therapy may be required before the effects are seen. Most of the improvement noted with RENOVA is seen during the first 24 weeks of therapy. Thereafter, therapy primarily maintains the improvement realized during the first 24 weeks.

With discontinuation of RENOVA therapy, a majority of patients will lose most mitigating effects of RENOVA on fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin; **however, the safety and effectiveness of using RENOVA daily for greater than 48 weeks have not been established.**

Application of larger amounts of medication than recommended will not lead to more rapid or better results, and marked redness, peeling, or discomfort may occur.

Patients treated with RENOVA may use cosmetics but the areas to be treated should be cleansed thoroughly before the medication is applied. (See **PRECAUTIONS** section.)

HOW SUPPLIED:

RENOVA is available in these sizes:

NDC 0062-0185-00	20 gram tube
NDC 0062-0185-05	40 gram tube
NDC 0062-0185-03	60 gram tube

Storage: Store between 15° and 25°C (59° and 77°F). DO NOT FREEZE.

QUESTIONS: Physicians and Pharmacists can call 1-800-426-7762, from 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday.

Rx only.

DERMATOLOGICAL DIVISION
ORTHO PHARMACEUTICAL CORPORATION
Raritan, New Jersey 08869

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RENOVA®

(TRETINOIN EMOLLIENT CREAM)

0.05%

RENOVA® (re-NO-vah)
Generic Name: Tretinoin Emollient Cream (0.05%)
FOR TOPICAL USE ON THE FACE ONLY

Patient Information

What is the Most Important Information about RENOVA?

RENOVA is a serious medication. It does not eliminate wrinkles or repair sun-damaged skin. It may help treat fine wrinkles, spotty discoloration, and rough feeling skin, but it does not "cure" these conditions. RENOVA should only be used under supervision of your health care provider as part of a broad skin care program. This program should include avoiding direct sunlight (by using protective clothing and sunscreens with a minimum SPF of 15) and using other moisturizing facial creams that do not contain tretinoin.

You should use RENOVA only at bedtime. Do not use drying skin care products. Use the smallest amount of RENOVA needed and avoid getting it in your eyes, ears, nose or mouth.

WARNING: Do not use RENOVA if you are pregnant or attempting to become pregnant. Avoid sunlight and any other medicines that may increase your sensitivity to sunlight (see below).

RENOVA has not been studied in people who are over 50 years of age or in people with moderately or darkly pigmented skin.

What is RENOVA?
(WHAT CAN I EXPECT FROM RENOVA?)

RENOVA is a serious medication that may help treat but will not "cure" fine wrinkles, spotty skin discoloration, and rough feeling skin.

Studies show that after 24 weeks, about 30% of the people who used RENOVA for fine wrinkles or spotty discoloration had moderate improvement, another 35% had minimal improvement and 35% had no improvement. About 16% of the people who used RENOVA for rough skin had moderate improvement, 35% had minimal improvement, and 49% had no improvement. There is no evidence that RENOVA treats coarse skin, deep wrinkles, yellowing skin, or other skin care problems.

RENOVA should be used as part of a broad skin care program. This program should include avoiding direct sunlight (by using protective clothing and sunscreens with a minimum SPF of 15) and using other moisturizing facial creams that do not contain tretinoin. Many people can achieve desired effects by using this program without using RENOVA. You should not use RENOVA until you have tried a broad skin treatment program without RENOVA.

When you use RENOVA, improvement in fine wrinkling, spotty skin discoloration and rough skin is not immediate and occurs gradually over time. Generally, you may notice some effects in 3 to 4 months. The effects are usually most noticeable at about 6 months with little additional improvement after that time. If RENOVA treatment is stopped, the improvement will gradually diminish.

The safety of using RENOVA daily for more than 48 weeks has not been established.

Who Should Not Use RENOVA?

You should not use RENOVA if you are sunburned or highly sensitive to the sun, if you have eczema, or if your skin is irritated. RENOVA can cause increased skin irritation and increased susceptibility to sunburn.

Since RENOVA may make your skin more sensitive to sunlight, you should tell your health care professional if you are also using other medicines that increase sensitivity to sunlight because you should not be using RENOVA with these medicines. These include but are not limited to: thiazides (used to treat high blood pressure), tetracyclines, fluoroquinolones or sulfonamides (used to treat infection), and phenothiazines (used to treat serious emotional problems). If you are taking any prescription medicines, non-prescription medicines or using any facial creams, check with a health care professional to make sure they do not interact with RENOVA.

Pregnancy Warning: Safe use during pregnancy has not been shown. There are reports of birth defects with laboratory animals and humans that were given tretinoin by mouth. You should not use RENOVA if you are pregnant or trying to become pregnant.

It is not known if RENOVA is passed to infants through breast milk. Safe use in children has not been shown.

The safety and effectiveness of RENOVA for people over age 50 or with darker skin coloration has not been proven.

How Should I Use RENOVA?

You should apply RENOVA to your face once a day before retiring using only enough to cover the entire affected area lightly. Gently wash your face with a mild soap, pat the skin dry, and wait 20 to 30 minutes before applying RENOVA. Apply a pea-sized amount of cream to cover your entire face. You may feel a warmth or slight stinging when RENOVA is first applied.

You must be especially careful when applying the cream to avoid your eyes, ears, nostrils, or mouth. RENOVA may cause severe redness, itching, burning, stinging, and peeling if applied to these areas.

Using larger than necessary amounts of RENOVA will not speed results and can cause an overdose. An overdose can result in red and peeling skin as well as some pain or discomfort.

You may use cosmetics after applying RENOVA. Make sure to clean your face thoroughly before applying RENOVA again.

What Should I Avoid While Using RENOVA?

RENOVA increases your sensitivity to sunlight. Avoid sunlight as much as possible. Use protective clothing and a sunscreen with a minimum SPF of 15. Do not sunbathe or use sunlamps. If you are sensitive to sunlight or have a job that requires you to be out in the sun for long periods, you must use extreme caution.

While using RENOVA, avoid any products that can dry or irritate the skin. For example, avoid products applied to the skin that contain alcohol, spices, or lime. Also, avoid cleansers, hair removal, or other products that can irritate the skin.

What Are the Possible Side Effects of RENOVA?

The most common side effects are skin reactions. Itching, red, and dry skin have been reported. So have burning, stinging, and peeling skin. These are most often mild and are most common when treatment is started.

How Can I Get Additional Information?

This leaflet summarizes the most important information about RENOVA. If you would like more information, talk to your doctor or other health care provider. There is also a leaflet written for health professionals that your pharmacist can provide for you.

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