PRODUCT MONOGRAPH

[Pr]RENOVA®

Tretinoin Emollient Cream 0.05%, House Std.

Agent for the treatment of photodamaged skin

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PRODUCT MONOGRAPH

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Tretinoin Emollient Cream 0.05%, House Std.

PHARMACOLOGIC CLASSIFICATION

Agent for the treatment of photodamaged skin

CLINICAL PHARMACOLOGY

RENOVA tretinoin emollient cream 0.05% significantly reduces clinical signs of photodamaged skin such as fine wrinkles, mottled hyperpigmentation, and roughness.

While the exact mechanism of action of RENOVA emollient cream 0.05% is unknown, the clinical improvements are accompanied by the following histologic changes: increased epidermal and granular layer thickness, reduced melanin content, and stratum corneum alterations.

INDICATIONS AND CLINICAL USE

RENOVA tretinoin emollient cream 0.05% is indicated for the treatment of fine wrinkling, mottled hyperpigmentation, and roughness of the skin. These signs are usually associated with photodamaged (sun-damaged) skin and intrinsic aging, but may be associated with other conditions.

The safety and efficacy of RENOVA emollient cream 0.05% for the prevention or treatment of actinic or solar keratoses have not been established.

CONTRAINDICATIONS

RENOVA tretinoin emollient cream 0.05% 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 tretinoin emollient cream 0.05% should be used under medical supervision as part of a comprehensive skin protection program, including use of sunscreen products and protective clothing.

Excessive use of RENOVA emollient cream 0.05% should be avoided. RENOVA emollient cream 0.05% should be kept away from the eyes, mouth, angles of the nose, or mucous membranes. Topical use may induce severe local erythema, pruritus, burning or stinging, 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.

Use in Pregnancy

Topical tretinoin should be used by women of childbearing years only after contraceptive counselling. It is recommended that topical tretinoin should not be used by pregnant women.

There have been a few reports of birth defects among babies born to women exposed to topical tretinoin during pregnancy. To date, there have been no adequate and well-controlled prospective studies performed in pregnant women and the teratogenic blood level of tretinoin is unclear. However, a retrospective cohort study of babies born to women exposed to topical tretinoin during the first trimester of pregnancy found no excess birth defects among these babies when compared with babies born to women in the same cohort who were not similarly exposed.

Oral tretinoin has been shown to be teratogenic and fetotoxic in rats when given in doses 1000 and 500 times the topical human dose, respectively.

In nine (9) out of ten (10) topical teratology studies of tretinoin conducted in rats and rabbits using several formulations, there has been no evidence of teratogenicity. In one (1) out of ten (10) studies, there was an increase in fetal malformations; however, a clear causal relationship of topical tretinoin and these findings could not be established. In a repeat of this study, there were no fetal malformations. Topical tretinoin can produce treatment-related fetal effects

(delayed ossification of bones and an increase in supernumerary ribs). The fetal no-effect dose is 1.0 mg/kg/day (200 times the recommended clinical dose). [See **TOXICOLOGY** - Reproduction and Teratology subsection]

Nursing Mothers

It is not known whether tretinoin is excreted in human milk. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

PRECAUTIONS

General

If a reaction suggesting sensitivity, chemical irritation, or a systemic adverse effect should occur, use of RENOVA tretinoin emollient cream 0.05% should be discontinued.

Exposure to sunlight and sun lamps should be avoided or minimized during the use of RENOVA because of heightened susceptibility to UV radiation as a result of the use of tretinoin. **Patients who may be required to have considerable sun exposure due to occupation, and those inherently sensitive to the sun should exercise particular caution**. Use of sunburn protectant products with a SPF of at least 15 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.

Carcinogenesis

The mutagenic potential of tretinoin was evaluated in the Ames assay and the *in vivo* mouse micronucleus assay, both of which were negative. In a lifetime study of topical tretinoin in CD-1 mice, there was no evidence of carcinogenic potential. Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of weakly carcinogenic light from a solar simulator. Although the significance of these studies to man is not clear, patients should avoid or minimize exposure to sun.

Information for Patients

A patient information leaflet has been prepared and is included with each package of RENOVA emollient cream 0.05% (see PATIENT PACKAGE INSERT section for text). The skin of certain sensitive individuals may become excessively

red, swollen, blistered, or crusted. RENOVA emollient cream 0.05% should be discontinued if patients experience severe or persistent irritation, and they should be advised to consult their physician.

Drug Interactions

Concomitant topical medication, medicated or abrasive soaps, shampoos and cleansers, cosmetics that have a strong drying effect, and products with high concentrations of alcohol, as well as astringents and products that may irritate the skin, should be used with caution because they may increase irritation with RENOVA emollient cream 0.05%.

ADVERSE REACTIONS

In double-blind, vehicle-controlled studies involving 199 patients who received RENOVA tretinoin emollient cream 0.05% for facial photodamage, adverse reactions associated with the use of RENOVA emollient cream 0.05% were limited primarily to the skin. Local reactions such as peeling or dry skin, burning or stinging, erythema, and pruritus were reported by most subjects during therapy with tretinoin emollient cream. These signs and symptoms were usually of mild to moderate severity and were generally well tolerated. These skin reactions occurred early in therapy and, except for dryness and peeling which tended to persist during therapy, generally decreased over the course of therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

RENOVA tretinoin emollient cream 0.05% is indicated 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 this drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION

RENOVA tretinoin emollient cream 0.05% should be applied once daily at bedtime, to lightly cover the entire face. In some cases, it has been necessary to temporarily discontinue therapy or to reduce the frequency of application. When the patient is able to tolerate the treatment, therapy can be resumed or the frequency of application can be increased.

Improvement in facial photodamage with RENOVA emollient cream 0.05% treatment occurs gradually over the course of therapy. Six months of therapy may be required before definite beneficial effects are seen.

Patients treated with RENOVA emollient cream 0.05% should use an effective sunscreen with a minimum SPF of 15 as well as protective clothing when exposure to the sun cannot be avoided.

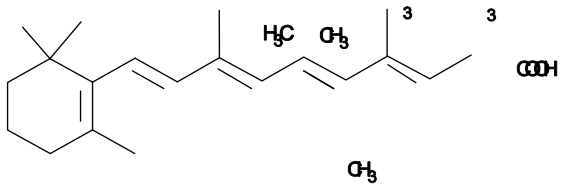
PHARMACEUTICAL INFORMATION

(i) DRUG SUBSTANCE

Common Name: tretinoin

Chemical Name: retinoic acid, all-*trans*-retinoic acid

Structural Formula:



TRETINOIN

Molecular Weight: 300.44

Molecular Formula: $C_{20}H_{28}O_2$

Description:

Tretinoin, a retinoid, appears as a yellow to light orange crystalline powder having a characteristic odour. Tretinoin is soluble in dimethyl sulfoxide, slightly soluble in polyethylene glycol 400, octanol, and ethanol (100%), practically insoluble in water and mineral oil, and insoluble in glycerin.

(ii) COMPOSITION

RENOVA emollient cream 0.05% contains the active ingredient tretinoin, at a concentration of 0.05% w/w in a formulation of light mineral oil, sorbitol solution, hydroxyoctacosanyl hydroxystearate, methoxy PEG-22/dodecyl glycol

copolymer, PEG-45/dodecyl glycol copolymer, stearoxytrimethyl-silane and stearyl alcohol, dimethicone 50cs, fragrance, methylparaben, edetate disodium, quaternium-15, butylated hydroxytoluene, citric acid (monohydrate) and purified water.

(iii) STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C and 25°C. DO NOT FREEZE.

AVAILABILITY OF DOSAGE FORMS

RENOVA tretinoin emollient cream 0.05% is a yellow cream that has a characteristic floral odour. The cream contains 0.5 mg tretinoin per gram and is available in tubes containing 20 grams.

RENOVA emollient cream 0.05% is a prescription drug (Schedule F).

INFORMATION FOR THE CONSUMER

PATIENT PACKAGE INSERT

RENOVA* tretinoin emollient cream 0.05%

RENOVA tretinoin emollient cream is a yellow cream with a light, pleasant fragrance. It contains 0.05% tretinoin and is available in 20 gram tubes.

RENOVA emollient cream 0.05% improves fine wrinkling, spotty pigmentation, and roughness sometimes seen in skin which has been chronically overexposed to the sun. Your doctor has prescribed RENOVA emollient cream 0.05% for you because your skin exhibits some or all of these signs.

RENOVA emollient cream 0.05% is available only with your physician's prescription. It should be used under medical supervision as part of a comprehensive skin protection program, including the use of sunscreen products and protective clothing.
Use only as specifically directed. Do not alter the dosage or frequency of application unless ordered to do so by your physician.

If you are a female of childbearing age, you should only use RENOVA tretinoin emollient cream 0.05% after consulting your doctor about contraceptive counselling. If you are pregnant you should discontinue use of RENOVA emollient cream 0.05%.

DO NOT USE THIS MEDICATION IF:

You have already used any products containing tretinoin and have developed an allergy or intolerance to it.

PROPER USE OF THIS MEDICINE

RENOVA tretinoin emollient cream 0.05% should be applied in the evening before bedtime, as follows:

- Gently wash your face using a mild soap containing no medications. Pat your face dry with a towel. Do not rub. Rubbing is abrasive to the skin.
- Allow up to 20 to 30 minutes for your face to dry before applying RENOVA emollient cream 0.05%. This may help decrease the likelihood of developing skin irritation.
- Squeeze a "pea-size" amount of RENOVA emollient cream 0.05% on your fingertip.
- Gently smooth RENOVA emollient cream 0.05% on your entire face until the cream vanishes. Do not over-apply RENOVA emollient cream 0.05%. The "pea-size" amount is sufficient for the treatment of sun-damaged skin. Use of larger quantities of RENOVA emollient cream 0.05% may increase your chances of developing skin irritation and will not necessarily speed up the improvement process.
- Do not place RENOVA emollient cream 0.05% in your eyes, mouth, angles of the nose, or mucous membranes. If you get RENOVA emollient cream 0.05% in your eyes by mistake, rinse your eyes several times with lukewarm water. If the irritation continues, contact your physician.
- Do not spot treat.
- Do not wash your face after applying RENOVA emollient cream 0.05%. Allow the areas treated with RENOVA emollient cream 0.05% to remain undisturbed overnight.
- Upon wakening the next morning, you may wash your face with a mild soap that contains no medications.
- Avoid or minimize exposure to sunlight and sun lamps because RENOVA heightens the susceptibility of your skin to the adverse effects of the sun.
- Use of sunburn protectant products with a sun protection factor (SPF) of at least 15 and protective clothing over treated areas is recommended when exposure cannot be avoided. The sunscreen should be re-applied after each time you have been swimming.
- During the course of therapy with RENOVA emollient cream 0.05%, avoid using preparations that have an abrasive, drying, or peeling effect, including soaps, shampoos, cosmetics, perfumes, and astringents (especially those containing alcohol, lime, or spices).
- Three to six months of treatment may be necessary before beneficial effects are seen.

SIDE EFFECTS

Along with its intended action, any medication may cause unwanted effects. The following side effects may occur: dry or peeling skin, burning, stinging, redness, or itching.

These side effects, with the exception of dry or peeling skin, usually occur early in the course of treatment. They are usually well tolerated and generally decrease over time.

The use of a non-alcohol-containing moisturizer may reduce the chance of side effects.

THIS MEDICINE WAS PRESCRIBED TO TREAT YOUR SPECIFIC MEDICAL PROBLEM AND IS FOR YOUR USE ONLY. DO NOT SHARE IT WITH OTHERS.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

If you need any further information, ask your physician or your pharmacist.

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PHARMACOLOGY

Retinoids, including all-*trans*-retinoic acid (tretinoin) are known to have profound effects on cell differentiation in skin. In animal studies, all-*trans*-retinoic acid has been demonstrated to cause formation of new connective tissue in the dermis of photodamaged skin in the hairless mouse. All-*trans*-retinoic acid also normalizes abnormal follicular keratinization in mice and rabbits and induces marked epidermal hyperplasia in mice and guinea pigs. In rhino mice, all-*trans*-retinoic acid alters the composition of epidermal and stratum corneum keratins, decreases the expression of filaggrin and increases the quantity of a non-keratin glycoprotein. No effect of all-*trans*-retinoic acid was observed in a model of skin inflammation (arachidonic acid ear edema) in mice.

Non-dermatological tests demonstrated that single administrations of the drug caused no serious effects on the central nervous system, cardiovascular and pulmonary systems in the animal species, for the doses and test systems utilized. *In vitro*, all-*trans*-retinoic acid also lacked activity against various microorganisms and pancreatic phospholipase A_2. These results suggest that all-*trans*-retinoic acid acts predominantly on skin and does not possess significant pharmacologic effects on three non-cutaneous organ systems after acute administration.

All-*trans*-retinoic acid was readily absorbed from the gastrointestinal tract. The absolute bioavailability of the compound was about 40%. When topically applied to mice, retinoic acid rapidly penetrated into and through the epidermis layer into the dermis and the amount absorbed was dose related. The absorption of radiolabeled retinoic acid after dermal application to rhesus monkeys, as calculated from urinary recoveries of radioactivity, was about 10% from normal, intact skin and 48% from dermatitic skin. The percutaneous penetration of retinoic acid was greater in mice when applied in an acetone base than in monkeys when applied in a commercial (RETIN-A*), cream. Comparatively, absorption is generally less in humans. It is transported in blood with albumin. The compound or its metabolites was widely distributed to a variety of tissues, with liver, kidney, intestine, and lungs being major tissue targets. Retinoic acid was extensively metabolized by processes which include isomerization, hydroxylations, side chain shortening, oxidation and epoxidation of the cyclohexane ring, and conjugation.

The elimination kinetics of systemic retinoic acid were dose dependent and triphasic. A rapid distributional phase was followed by a slower, prolonged elimination phase which increased in duration as the dose increased, and then a third, more rapid phase. In most studies, the elimination was non-exponential. The middle plateau phase indicated the presence of a saturable elimination process, probably a saturated metabolic pathway.

Retinoic acid was eliminated via urinary and biliary/fecal routes. The side chain terminal carboxy group was excreted, in part, as expired CO_2.

CLINICAL PHARMACOLOGY

Although the exact mode of action of tretinoin is unknown, topical tretinoin produced dose-dependent structural changes in the epidermis consisting of increased epidermal and granular cell thickness, stratum corneum alterations, and a reduction in melanin content.

Percutaneous absorption of tretinoin in an emollient cream formulation was assessed in healthy male subjects after a single application and after repeated daily applications. In all subjects, absorption was minimal (i.e. <2%) and endogenous concentrations of tretinoin and its major metabolites were unaltered (maximum absorption of radioactivity in one study did not exceed an average of approximately 7% to 8% of the applied dose). In addition, its estimated volume of distribution was very large (31 liters). One study in 6 male subjects with a single topical application of ^{3}H-labeled tretinoin in 0.05% cream formulations demonstrated low absorption (<2%), as measured by the ^{3}H content of urine and feces over a 72-hour period after application. In this same study, 6 male subjects who were treated with unlabeled 0.05% tretinoin cream formulations for 28 days demonstrated identical absorption (<2%) after application of ^{3}H-tretinoin cream on day 29. Baseline plasma concentrations of tretinoin and its metabolites were unaffected in these subjects. In a separate study, absorption in 3 female subjects and 1 male subject, who had been using tretinoin cream for at least a year, was slightly lower after a single application of ^{3}H-labeled cream, as measured by the ^{3}H content of urine and feces. In studies with other tretinoin formulations, including ointments and solutions, absorption (under occlusion) ranged from 2.3 - 8.0% of the dose in acne and psoriasis patients.

A physiological-based pharmacokinetic model was used to estimate internal exposure after application of tretinoin cream. The model is based on physiological and biochemical processes which were used to describe the physiological disposition of tretinoin. The model incorporated variable drug input (topical, intravenous, and oral administration), physiological distribution, saturable metabolism (glucuronidation, oxidation, and isomerization), and excretion in urine and feces with enterohepatic recycling. Exposure was estimated for plasma, liver, gut, intestinal lumen, fat, skin, richly perfused tissues, slowly perfused tissues, placenta, and embryo under conditions of anticipated clinical use and under conditions of overuse. The estimated internal exposure of tretinoin and metabolites after topical application of RENOVA tretinoin emollient cream 0.05% under conditions of overuse (worst case) would be 10,000 times lower than the exposure in animal safety studies (see **PRECAUTIONS**).

CLINICAL TRIAL EXPERIENCE

In clinical trials involving 349 Caucasian subjects aged 30-50 years treated with RENOVA tretinoin emollient cream 0.05% or its vehicle, three primary efficacy variables were assessed at the end of the 6-month, double-blind treatment period: investigator's global evaluation at the end of therapy, the change from baseline to the end of therapy in the investigator's evaluation of the overall severity of photodamage, and the overall subject self-assessment at the end of therapy. As illustrated below, for each of these primary efficacy variables, a greater percentage of subjects improved with RENOVA emollient cream 0.05% than with its vehicle. In addition, fine wrinkling, mottled hyperpigmentation, and roughness of facial skin each improved in a greater percentage of subjects treated with RENOVA emollient cream 0.05% than with its vehicle.

	Percent of Subjects Improved	
	RENOVA cream	Vehicle
Primary Efficacy Variables		
Investigator's Global Evaluation	78%	43%
Investigator's Evaluation of Overall Severity of Photodamage	68%	38%
Overall Subject Self-Assessment	81%	50%
Clinical Signs		
Fine Wrinkling	65%	38%
Mottled Hyperpigmentation	60%	45%
Roughness	53%	35%

Computer-generated skin replica assessments of skin topography also showed greater improvement for the RENOVA emollient cream 0.05%-treated subjects than for vehicle-treated subjects. A greater reduction from baseline to the 6-month evaluation in the skin replica measures for the RENOVA emollient cream 0.05%-treated subjects than for vehicle-treated subjects reflects greater improvement in skin wrinkling and roughness in RENOVA emollient cream 0.05%-treated subjects.

RENOVA emollient cream 0.05% treatment resulted in increased epidermal thickness, increased granular layer thickness, and stratum corneum compaction as determined by histological comparison of the 6-month treated biopsied skin to the biopsies taken at baseline. There was also a greater reduction in melanin content for the RENOVA emollient cream 0.05%-treated skin than vehicle-treated skin.

TOXICOLOGY

Acute Toxicity

The acute toxicity potential of various tretinoin formulations was evaluated following oral administration to mice, rats, and dogs, topical application to rabbits, and intravenous administration in mice and rats. The LD_{50} values of tretinoin are summarized below:

Species	Route of Administration	Concentration of Drug	LD_{50} mL/kg
Mouse	p.o.	pure drug	>40 (>5000 mg/kg)
	p.o.	0.025% TEC*	>15 (> 3.6 mg/kg)
	p.o.	0.1% Cream	>44.0
	p.o.	0.1% Gel	19.0
	i.v.	0.1% Gel	5.2
Rat	p.o.	0.025% TEC*	>15
	p.o.	0.05% Gel	20.2
	p.o.	0.1% Gel	20.9
	i.v.	0.1% Gel	8.7
Dog	p.o.	0.1% Gel	>10
Rabbit	topical	0.1% Gel	> 9.4

* **TEC** = Tretinoin Emollient Cream formulation.

Side effects in rodents include alopecia, reduced food consumption, decreased body weight gain or weight loss, lethargy, and decreased motor activity.

TEC formula (0.025% tretinoin) was applied for 24-hour exposures to the abraded skin of rabbits at dose levels of 0.5 and 0.05 mg/kg tretinoin in an acute dermal toxicity study. These levels are comparable to approximately 80 and 8 times the anticipated human dose of tretinoin on a weight basis, and 600 and 60 times the daily human dose on a weight-surface area basis.

Dermal erythema, edema, and epithelial thickening were found in animals of both sexes. Decreased red blood cell count, decreased hematocrit and hemoglobin, and one ounce total protein were observed in high-dose-treated males.

Long-Term Toxicity (subacute and chronic)

Subchronic toxicity studies were performed in rats and rabbits. In one of the studies involving rats, retinoic acid was administered i.p. for 11 or 18 days at daily dose levels of 8.7, 17.5, and 26.2 mg/kg. There was a dose-related decrease in body weight gain and slight decreases in erythrocytes, hemoglobin, and hematocrit. In addition, there was thickening of the epidermis, sometimes with hyperkeratosis, in all rats, and a dose-related increase in bone fractures. Examination of the liver revealed some enlarged Kupffer cells.

Doses of 0.02, 0.1, and 0.5% retinoic acid were applied topically onto the shaved skin of the back of rats in the second study. Body weight gain was decreased in the high-dose group and histological examination revealed dose-related hyperkeratosis, leukocyte infiltration, and necrotic inflammation in the high-dose group.

In the third study, retinoic acid was added to the diet of rats for 12 weeks at doses of 0, 0.4, 2.0, or 10.0 mg/kg/day. There was a slight decrease in erythrocyte count, hemoglobin and hematocrit, and elevation of alkaline phosphatase levels in treated animals.

Organ weight data showed significant increases in the relative and absolute weights of the liver in the mid- and high-dose groups, and histopathological studies revealed increased basophilia of the hepatic cytoplasm in mid- and high-dose animals.

Retinoic acid was applied topically to the backs of albino rabbits at doses of 0, 0.1, 0.5, or 1.0 mL/kg/day for 3 weeks. Findings included dose-related erythema, hyperkeratosis, slight dose-related decreases in hematocrit and hemoglobin, and epidermal hyperplasia with associated inflammation in all treated groups.

A six-week subacute dermal toxicity study was performed in rabbits. Within this period, dosage levels of 0.1, 0.5, and 1.0 mL/kg/day of retinoic acid solution (0.1%) were applied to the abraded and intact skin of the animals. The backs of these animals were not washed at the end of the day, although the backs of an additional group at the high-dose level (1.0 mL/kg/day) were washed daily. These daily doses were estimated to be 3-30 times the calculated maximum clinical dose. Locally there was marked erythema, hyperkeratosis, and loss of elasticity. These responses were dose-related and reached their maximum in about three weeks. The washed high-dose group had less localized reaction than the unwashed high-dose group. In those animals studied, four weeks after the application of retinoic acid was discontinued, the localized reactions subsided. Little evidence of irritation remained at the end of the observation period.

Other findings were considered to be indirectly attributable to the irritation produced by the test materials. These dose-related effects included impaired growth, depression of the erythrocyte-hemoglobin-hematocrit system, and accelerated sedimentation rates. An increased frequency of gross lesions in all treated groups was observed at necropsy.

Ophthalmologic and radiologic examinations, and the chemistry assays gave no indication of toxicity. Tissue histopathology only revealed changes in the skin. There was no evidence found of systemic toxicity directly attributable to topical application of the retinoic acid solution. Those changes that did occur were considered related to the known local irritant properties of retinoic acid.

Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of ultraviolet radiation. The significance to humans is not clear.

Four groups of 60 hairless mice each were used in the 18-month study. Groups II, III, and IV were treated daily with simulated solar ultraviolet radiation (UVR). The mice were exposed for 2 hours on each of 196 consecutive days to 180 J/M^2/day erythema effective energy (approximately one-half human skin erythema dose of UVR). After each UVR exposure, the groups were painted topically with 100 µL of either the vehicle alone (methanol), or 0.001% retinoic acid (RA), or 0.01% RA in methanol.

Group I received the vehicle alone without UVR. Beginning at 20 weeks, the two groups III and IV receiving UVR plus RA developed a substantial number of tumours; there were no tumours in Group I. The mean latent period for tumour appearance in the vehicle plus UVR Group II was applied 30 weeks longer than the mean latent periods of the RA-treated groups. The mechanism of the RA-enhanced photocarcinogenesis is not yet known.

In separate tests, the investigators found no evidence of RA phototoxicity in mouse skin *in vivo*.

Special toxicity studies performed in rabbits and guinea pigs indicate that most tretinoin formulations (including tretinoin emollient cream 0.05%) are mild to moderate dermal irritants to rabbit skin, minimal to non-irritants in the rabbit eye, and non-sensitizers in the guinea pig.

Tretinoin also showed no potential for producing a phototoxic response in the guinea pig model.

Dermal toxicity studies in humans have shown that the retinoic acid solution (0.1%) did not cause contact sensitization, phototoxicity, or photosensitization in any of the subjects investigated. Further studies have shown the expected local effects of erythema, tenderness, and pooling. However, there was no evidence of systemic toxicity.

Kligman, et al. studied the histology of normal skin treated with 0.1% Vitamin A acid in an alcoholic vehicle, and reported :

> As initial clinical inflammation developed, the epidermis thickened (acanthosis) and the cornified cells retained their nuclei (parakeratosis). A quite characteristic change was the intercellular accumulation of fluid causing the cell membranes to be pushed apart.

> This prominent intercellular edema was not usually accompanied by evidence of cell damage. Surprisingly, little inflammatory cell infiltrate was seen in the dermis; these changes related to mild inflammation.
>
> With high concentrations, there may be severe epidermal damage with vesiculation. In the chronic phase, after weeks or months of application, the characteristic findings were moderate acanthosis, a decidedly thickened and conspicuous granular cell layer, and a thin, loose stratum corneum which was frequently lost in sectioning. Again dermal inflammatory changes were scarcely discernible.

Studies of retinoic acid in topical application to human skin have produced no evidence of toxic effects other than local irritation. One investigator who applied 0.1% retinoic acid in fatty cream topically to 53 patients for as long as a year of continuous therapy reported occasional skin irritation "which disappears quickly".

Studies have been conducted to determine the amount of tretinoin that can penetrate human skin when it is applied topically. These studies involved application of C^{14}-tagged tretinoin topically to volunteers with normal skin, and others with psoriasis or acne whose skin was irritated by repeated applications of tretinoin before the studies with radioactive material were conducted.

In normals, absorption of the solution was greater (1.8 x) than with the ointment. Absorption after single administration was increased six-fold in subjects with acne, and increased 37x in these subjects, on repeated (10 day) application, to an average maximum absorption of 26% of the administered dose.

Based on the recovery of radioactivity from the site of application, the average maximum absorption with the ointment was 4% in normal subjects, 6% in subjects with psoriasis following single administration, and 14% in the same subjects following repeated (10 day) administration. The average maximum absorption with the solution was 14% in normal subjects, 20% in subjects with acne following single administration, and 1% following repeated 10 day administration. These figures are reasonable estimates for maximum possible absorption; however, they may tend to overestimate the actual extent of absorption because of the technical problems associated with quantitative removal of the applied dose 6 hours after application.

This study has shown that, under the time limits stated, the average maximum extent of absorption of retinoic acid from a petrolatum base ointment in subjects with psoriasis is approximately 8% of the dose, and does not exceed 14% of the administered dose. The average maximum extent of absorption of retinoic acid from a solution in subjects with acne is approximately 26% of the administered dose, and does not exceed 31% (on the average) of the administered dose.

Knowing the greatest amount absorbed in one individual (58%), the "high average" absorption (31%), and the maximum amount applied topically (rounded off to 1.6 g), it is possible to calculate a "safety index" as follows:

Dose applied	1.6 g	1.6 g
Patient's weight	50 kg	50 kg
Concentration of drug	0.05 % 0.05%	
Extent of absorption	31 %	58 %
Amounts absorbed	0.005 mg/kg	.009 mg/kg
No effect dose (in rats)*	1.0 mg/kg	1.0 mg/kg
Safety Index	200:1	111:1

* Species most sensitive to teratogenic effects.

Although the foregoing figures are based on the most extensive application that might occur (entire face, back, and chest) and the highest absorptions determined experimentally, it is worth noting that even if 100% were absorbed, the safety factor would still be in excess of 62-fold, based on the 1 mg/kg systemic dose determined to be safe in pregnant rats. If the concentration of tretinoin were doubled to 0.1%, the safety factor would still be more than 31-fold with 100% absorption. At 0.1% concentration the safety factor would be 55:1 when calculated in relation to the tested maximum absorption through damaged skin.

Mutagenicity

The mutagenic potential of tretinoin was evaluated in the Bacterial/Microsomal Activation Assay (Ames Assay) using test strains of *Salmonella typhimurium* and *E. Coli* with and without metabolic activation. Tretinoin exhibited no mutagenic effect on the test organisms.

Reproduction and Teratology

In a dermal rat teratogenicity study, animals received 0.1 or 1.0 mL/kg/day of 0.05% tretinoin gel which corresponds to 0.05 or 0.5 mg/kg/day pure drug applied topically throughout organogenesis. There was no evidence of maternal, embryo or fetal toxicity, or teratogenicity. In the high dose, there was an increase in the anatomical variations of incomplete ossification of parietal, interparietal, and supraoccipital bones of the skull. These effects are not considered to be teratogenic responses.

Topical administration of all-*trans*-retinoic acid to pregnant rats at dose levels of 1, 2.5, or 5 mg/kg/day during the period of organogenesis (days 6 - 16 of gestation) was not teratogenic even at maternally toxic doses ($\geq$ 2.5 mg/kg). There was evidence of fetal toxicity at 5 mg/kg; an increase in the incidence of supernumerary ribs was noted, as was a decrease in body weight.

A dermal rabbit study was conducted to evaluate the teratogenic and/or embryotoxic potential of three 0.1% tretinoin formulations: ointment, cream and alcoholic solution. Drug was applied to a shaven area of the backs of animals in the following amounts: 150 and 600 mg/kg for the ointment, 50 and 200 mg/kg for the cream, 0.4 and 1.6 mL/kg for the solution. Well-defined erythema was recorded in all the animals receiving the high dose levels of both the ointment and cream from the second to the last day of treatment. A milder degree of erythema was seen in the animals treated with 1.6 mL/kg of the solution. Slight edema was noted only in the high-dose ointment animals on examination at the end of the treatment period. In all cases, the adverse reaction quickly regressed and was no longer visible by the end of gestation. Dose levels of up to 600 mg/kg tretinoic acid ointment, 200 mg/kg retinoic acid cream, and 1.6 mL/kg retinoic acid solution had no teratogenic activity or adverse effects on weaning when rubbed onto the backs of New Zealand white rabbits daily from day 6 to day 18 of gestation. The cream and solution at the high dose levels did produce a slight increase in embryotoxicity, but it was thought unlikely that this would be reproduced in clinical practice.

In a separate dermal rabbit teratogenicity study, animals received 0.1 or 1.0 mL/kg/day of 0.05% tretinoin gel, which corresponds to 0.05 or 0.5 mg/kg/day pure drug, applied topically throughout organogenesis. Dose-related moderate to severe dermal irritation was observed in the dams. There was a slight increase in resorption in the high-dose group and a treatment-related increase in incomplete ossification of parietal bones, as was previously reported in rats. No evidence of teratogenicity was found.

A rabbit study utilizing topically applied dosages of 0.05 and 0.5 mg/kg/day of tretinoin (1 mL/kg/day of 0.005% and 0.05% RENOVA formulation, respectively) was conducted to assess embryo-fetal toxicity and teratogenic potential. The RENOVA formulation was not teratogenic at maternally toxic dosages of up to 0.5 mg/kg (100 times the clinical dose). Marked maternal toxicity (severe dermal irritation, decreased body weight) was observed at 0.05 and 0.5 mg/kg/day. At the high dose (0.5 mg/kg/day of tretinoin) increased incidence of spontaneous abortions and fetal toxicity (decreased body weight and increased resorptions probably secondary to maternal toxicity) were observed.

A rat study using an investigational topical formulation of tretinoin at dosages of 0.2, 0.5, and 1.0 mg/kg/day was conducted to assess embryo-fetal toxicity and teratogenic potential. Maternal toxicity was observed in all treated groups. No adverse effects on embryo-fetal viability, fetal body weights, or fetal morphology were observed at the doses tested.

A rabbit study utilizing topically applied dosages of the same investigational formulation of tretinoin in dosages of 0.2, 0.5, and 1.0 mg/kg/day was conducted to assess embryo-fetal toxicity and teratogenic potential. Rabbits wore Elizabethan collars during the treatment period. Maternal toxicity was observed in all treated groups. Evaluation of the

incidence of specific fetal findings revealed an association with the 0.5 and 1.0 mg/kg/day dosages. These included slight-to-moderate dilation of the lateral and/or third ventricles of the brain, and hydrocephaly, and, in these fetuses, cleft palate, hemorrhagic brain, or deformations of limb and/or rib. A causal relationship of topical treatment and these findings could not be established because the fetal observations were not consistently dose-dependent; oral and/or inhalation exposure could not be ruled out and hydrocephaly is known to occur spontaneously in rabbits. Therefore, a follow-up study was designed to clarify the etiology of the fetal alterations.

In the follow-up rabbit study, animals were exposed to topically applied dosages of 0.5 and 1.0 mg/kg/day of the investigational formulation of tretinoin for 6 hours/day, or 1.0 mg/kg/day for 24 hours/day. Animals exposed for 6 hours/day were restrained during the exposure period. Animals exposed for 24 hours/day were not restrained. Maternal toxicity was observed in all treated groups. No fetal abnormalities were observed in either group exposed. Therefore, the fetal alterations in the previous study may have been spontaneous events or the result of possible oral ingestion during the study.

Oral administration of tretinoin to pregnant rats at doses of either 1.0 or 2.5 mg/kg/day throughout organogenesis produced no maternal toxicity. The higher dose produced only a modest increase in intrauterine death. There was a treatment-related, but not dose-related, increase in the anatomical variations of increased thoracic ribs or sternebrae. Tretinoin at either dose did not interfere with implantation or fetal weight, nor did it produce a teratogenic response.

In another study, pregnant rats received a suspension of all-*trans*-retinoic acid orally at doses of 1, 2.5, 5, or 10 mg/kg/day on days 6 through 15 of gestation. At 10 mg/kg, an increase in the incidence of cleft palate was observed.

Orally administered tretinoin during pregnancy produces dose-dependent and stage-dependent fetal anomalies in several species. In Segment II oral and dermal teratology studies in Wistar rats, frank fetal malformations were observed only after oral administration of 10 mg/kg tretinoin, where one fetus in each of 3 litters showed cleft palate. No fetal malformations resulted after oral administration or dermal application of tretinoin at 1, 2.5, or 5 mg/kg doses. Oral and dermal doses of >2.5 mg/kg tretinoin produced an increased incidence of fetuses with skeletal variations (greater in oral), e.g. vestigial ribs. Skeletal variations, while treatment-related, are not categorized as teratogenic outcomes but as segmental variations of embryonic pattern formation and as such are not incompatible with normal development. While oral tretinoin produced a higher incidence of fetal effects than dermal tretinoin, the overall fetal no-observable-effect level by either dosage route is 1 mg/kg (200 times the estimated clinical dose). The findings in the two above-mentioned studies are consistent with results reported from numerous earlier studies.

Carcinogenesis

Tretinoin was administered dermally to CD-1 mice three days per week for 91 weeks at concentrations of 0 (untreated control or vehicle [Butylated Hydroxytoluene NF 0.05%; SD alcohol Type 40 - 190 proof]), 0.0008%, 0.017%, or

0.035% corresponding to 0.025, 0.05, or 1.0 mg/kg/dose (approximately 5, 100, and 200 times the anticipated clinical dose of 0.005 mg/kg/dose).

Microscopic evaluation of non-skin tissues revealed no statistically significant neoplastic changes among groups. Two carcinomas (one in the mid-dose group and one in the high-dose group) and five papillomas (three in the mid-dose group and two in the high-dose group) were observed on or adjacent to the treatment site. Two other carcinomas, distantly removed from the treatment site (one on the foreleg of a high-dose mouse and another on the ear of a low-dose mouse) were observed.

The two distinctly removed carcinomas were not considered drug related because they were not associated with the dosing site and their origins were from non-skin tissue. The cause of the carcinomas observed on or adjacent to the treatment site is not definitely known, but is believed to be spontaneous. The incidence of squamous cell carcinomas in this study is within the reported spontaneous incidence range (up to 2.5%) for female CD-1 mice. The five papillomas at or adjacent to the application site of the three mid- and two high-dose mice are believed to be a response to chronic severe irritation (eschar, scabbing, scaling) that was observed during the life of these animals at these dose levels. The severity of irritation observed at the application site of the high- and mid-dose mice was similar to and significantly greater than that observed at the low dose.

Considering that there was no definitive evidence of carcinogenicity of the skin or any other organ system in this study, topical administration of tretinoin does not present a carcinogenic risk to humans.

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