PRODUCT MONOGRAPH

PrREJUVA-A®

Tretinoin cream USP 0.025% w/w

AGENT FOR THE TREATMENT OF PHOTODAMAGED SKIN

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
www.stiefel.ca

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THERAPEUTIC CLASSIFICATION

AGENT FOR THE TREATMENT OF PHOTODAMAGED SKIN

ACTIONS AND CLINICAL PHARMACOLOGY

ACTION AND CLINICAL PHARMACOLOGY

Tretinoin, a member of the retinoid class of compounds, is both pharmacologically and structurally related to vitamin A, which regulates epithelial cell growth and differentiation. Retinoic acid may exert its effects at the molecular level by binding to specific steroid-like nuclear receptors known as retinoic acid receptors. Binding of retinoic acid to a retinoic acid receptor will promote events at the cellular level by regulating gene transcription and affecting activities such as cellular differentiation and proliferation, but the exact mechanism underlying these processes remain to be elucidated.

Topical tretinoin has been reported to correct many of the structural abnormalities of photo aged skin. Tretinoin has been shown to produce epidermal and dermal changes. At the epidermal level, tretinoin increased the epidermal thickness (acanthosis) and the mean granular layer, decreased tonofilament and desmosome strength and increased secretion of a glycosaminoglycan-like substance into the intercellular space. In addition, the cohesion of the epidermal cells and activity of the melanocytes were reduced.

Functional changes in the epidermis include an increase in trans-epidermal water loss and permeability. At the level of the dermis, vasodilatation and angiogenesis of the superficial vasculature, along with increased papillary dermal collagen, have been reported.

The long term (1 year) safety and efficacy of REJUVA-A® Cream (tretinoin cream USP 0.025% w/w) in the treatment of photo aging was evaluated during a double-blind, randomized, parallel group, multicentre, placebo controlled study. A total of 147 patients (110 active, 37 placebo) were entered; all were Caucasian with chronic, moderate to severe actinically damaged facial skin. The patients applied the medication over their entire face once a day before retiring and were evaluated by the investigators after 1, 3, 6, 9 and 12 months of therapy.

Significant clinical benefits were demonstrated for REJUVA-A® versus placebo:

1. Reduction in fine wrinkles from Month 3.
2. Reduction in moderate, moderately severe and severe coarse wrinkles from Month 6.
3. Reduction in the severity of dermatoses at Month 9.

In addition, histological findings demonstrated that skin treated with REJUVA-A® showed significant decrease in the thickness of the stratum corneum and increases in the thickness of the stratum granulosum and spinulosum. Skin receiving the placebo cream showed no significant difference in the thickness of the different epidermal strata.

INDICATIONS AND CLINICAL USE

REJUVA-A® (tretinoin cream USP 0.025% w/w) is indicated for the treatment of photo damaged skin (heliodermatitis).

The safety and efficacy of REJUVA-A® for the prevention and treatment of actinic keratosis has not been established.

Pediatrics (<18 years of age): Safety and effectiveness of REJUVA-A® in pediatric patients less than 18 years of age have not been established. Use in pediatric patients is not recommended.

Geriatrics (> 70 years of age): Safety and effectiveness of REJUVA-A® in patients greater than 70 years of age have not been established.

CONTRAINDICATIONS

REJUVA-A® is contraindicated in patients with known hypersensitivity to retinoids or to any ingredient contained in the preparation or component of the container. For a complete listing, see PHARMACEUTICAL INFORMATION, Composition.

WARNINGS

REJUVA-A® should be used as part of a comprehensive skin protection program, including use of sunscreen products and protective clothing.

REJUVA-A® IS INTENDED FOR EXTERNAL USE ONLY AND SHOULD BE KEPT AWAY FROM ABRADED SKIN, LIPS, MOUTH, EYES, NOSTRILS AND OTHER MUCOUS MEMBRANES BECAUSE OF ITS IRRITANT EFFECT. IN CASE OF ACCIDENTAL CONTACT WITH THE EYE AND IF SENSITIVITY OR CHEMICAL IRRITATION OCCURS, THE MEDICATION SHOULD BE DISCONTINUED. RINSE PROFUSELY WITH WATER AND REFER THE PATIENT TO THE OPHTHALMOLOGIST.

Care should be used when REJUVA-A® is applied to treat wrinkles around the eyes (Crow's feet) and mouth. Do not apply to eyelids. Avoid application to the angles of the nose, skin fold areas and nasolabial folds (if treatments in these areas are necessary, apply very sparingly with care not to let the medicine accumulate). 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 of eczematous skin and REJUVA-A® should only be used with utmost caution in patients with this condition.

REJUVA-A® should be used with caution in patients using medications that are known photosensitizers (see DRUG INTERACTIONS).

Fertility

There are no data on the effect of topical tretinoin on fertility in humans.

Special Populations

Pregnant Women

Topical tretinoin should not be used by pregnant women. Topical tretinoin is not recommended for women of childbearing years without the proper use of an effective method of contraception.

Observational studies of varying sample size involving a total of 1535 women presumed exposed to topical tretinoin during the first trimester of pregnancy did not detect an increased incidence of congenital abnormalities, including retinoic acid embryopathy or major structural defects.

Cases of temporally associated congenital abnormalities have been reported during clinical use of topical tretinoin during pregnancy, including the rare birth defect category, holoprosencephaly.

Orally administered retinoids are known teratogens, causing a high incidence of severe birth defects, and are contraindicated during pregnancy.

Nonclinical reproductive toxicity studies of topical retinoids have found evidence of developmental toxicity at doses ≥ 80-fold the anticipated clinical dose.

The magnitude of risk to the embryo/fetus from topical use of tretinoin is uncertain. When used in accordance with the prescribing information, there is an approximate 1% to 6% systemic absorption from topically administered tretinoin. However, even though systemic absorption is low from topically administered tretinoin, risk cannot be excluded since there may be other factors that contribute to an increased systemic exposure such as dose used, skin barrier integrity, concurrent use with other products, hypervitaminosis A and dietary intake of vitamin A and/or provitamin A (beta-carotene) or ingestion of these as supplements.

Nursing Women

It is not known whether tretinoin is excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the benefit of breastfeeding to the child and the benefit of the drug to the mother.

Pediatrics (<18 years of age)
Safety and effectiveness in pediatric patients less than 18 years of age have not been established, therefore REJUVA-A® cream is not recommended for use in this population.

PRECAUTIONS

General
Tretinoin has irritant properties, heightens susceptibility to ultraviolet light radiation, is sensitive to oxidation and is photolabile.

REJUVA-A® should be used with caution in patients with:
- a history of local tolerability reactions, photoallergy, or local hypersensitivity.
- a personal or family history of skin cancer.

Environmental Factors

As tretinoin may cause increased sensitivity to ultraviolet radiation, exposure to sunlight and sun lamps should be avoided or minimized during the use of REJUVA-A®.

Due to the potential for photosensitivity, resulting in a greater risk for sunburn, REJUVA-A® should be used with caution in patients with a personal or family history of skin cancer.

If a patient has sunburn, this should be resolved before initiating treatment with REJUVA-A®. If sunburn occurs while using REJUVA-A®, it is advisable to interrupt therapy until the severe erythema and peeling subside.

When exposure to strong sunlight cannot be avoided (e.g. patients whose occupations require considerable exposure to the sun) and those inherently sensitive to the sun are advised to use a broad spectrum sunscreen of at least SPF 15, to re-apply sunscreen regularly and to wear protective clothing over treated areas.

Weather extremes, such as wind or cold, may be more irritating to patients using tretinoin-containing products.

Skin

Due to the irritant nature of tretinoin, caution should be used when applying REJUVA-A® to sensitive areas of skin, such as the neck, or in patients with concomitant rosacea or perioral dermatitis.

The skin of certain sensitive individuals, particularly those with fair complexions, may become excessively red, edematous, blistered or crusted when exposed to REJUVA-A®.

If skin irritation (redness, peeling or discomfort) or effects of other treatments with irritating potential are present, this should be resolved before initiating treatment with REJUVA-A®.

Patients should be advised that excessive application will not improve efficacy, but may increase the risk of severe skin irritation. If severe irritation occurs, interrupt dosing to allow the skin to recover, and re-evaluate the dosing regimen with the patient.

Carcinogenesis and Mutagenesis

Carcinogenic studies have not been conducted with REJUVA-A®. Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of ultra violet radiation. 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 REJUVA-A® (see Information for the Consumer section).

DRUG INTERACTIONS

Concomitant application of oxidising agents, such as benzoyl peroxide, should be avoided since they may reduce the efficacy of topical tretinoin. If combination therapy is required, the products should be applied at different times of the day (eg, one in the morning and the other in the evening).

Cumulative Irritation

Concomitant topical medication should be used with caution during therapy with REJUVA-A® because cumulative irritation may occur. Particular caution should be exercised during concomitant use of preparations containing a peeling agent (such as sulfur, resorcinol, or salicylic acid) with REJUVA-A®. If irritation or dermatitis occur (redness, peeling or discomfort), reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

In patients whose skin has been subjected to procedures such as depilation, chemical hair treatments, chemical peels, dermabrasion or laser resurfacing, allow the skin to recover before initiating treatment with REJUVA-A®.

Cosmetics that have a strong drying effect, including products with high concentrations of alcohol and/or astringents, or that have a potential irritating effect (abrasive agents, products containing spices or limes, etc.) should be used with caution as cumulative irritation may occur.

Patients may use noncomedogenic, hypoallergenic, and oil-free cosmetic products.

Augmented Photosensitivity

Medications known to be photosensitizers (e.g., thiazides, tetracyclines, fluroquinolones, phenothiazines, sulphonamides) should be used with caution with REJUVA-A® because augmented photosensitivity may occur.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

In the long term clinical trial with REJUVA-A® , erythema and peeling/dryness were the most reported side effects in the REJUVA-A® group with only 5 of 110 patients from this group withdrawing because of adverse events (erythema and peeling).

The following very common adverse drug reactions (≥ 10%) have been reported in clinical trials involving topical tretinoin-containing products:

Skin and subcutaneous disorders: pain, burning sensation, tenderness, irritation or pruritus, application site erythema, skin exfoliation, application site stinging and dry skin.

The following adverse drug reactions (< 10%) have also been reported in clinical trials involving topical tretinoin-containing products:

Skin and subcutaneous disorders: edematous (1.1%), blistered (1.6%) or crusted skin (0.5%), contact dermatitis (2.2%).

If any of these effects occur, the medication should be discontinued until the integrity of the skin has been restored or the treatment schedule adjusted to the level the patient can tolerate. To date, all adverse clinical effects of tretinoin encountered have been reversible upon discontinuance of therapy. In many instances, re-institution of therapy with tretinoin failed to produce the adverse effect previously experienced.

Post-Market Adverse Drug Reactions

Immune system disorders: allergic reaction

Skin and subcutaneous disorders: skin hyperpigmentation, skin hypopigmentation, photosensitivity reaction, application site rash, application site edema/swelling, skin atrophy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

If topical medication is applied excessively, marked redness, peeling or discomfort may occur. If severe irritation occurs, suspend treatment and appropriate symptomatic measures should be taken.

REJUVA-A® contains 0.025% w/w tretinoin. Therefore, a 20 g tube would contain 5 mg tretinoin.

In case of suspected overdosage, management should be as clinically indicated or as recommended by the regional poisons centre, where available. Inadvertent oral ingestion of REJUVA-A® cream may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A including teratogenesis in women of childbearing years. Therefore, in such cases, pregnancy testing should be carried out in women of childbearing years.

DOSAGE AND ADMINISTRATION

REJUVA-A® is especially suitable for the treatment of sun sensitive Types I and II skin types* *e.g.,* fair skinned people with red or blond hair and blue or hazel eyes, who always burn easily, severely with no or minimal tanning.

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* Classification of Sun-Reactive Skin Types.
From: Textbook of Dermatology 4th Edition Edited by Rook A, Wilkinson DS, Ebling FJG, et al 1986; Chapter 39: 1554-1555

REJUVA-A® should be applied sparingly to the affected area once a day just before retiring. The area under treatment should be thoroughly cleansed with a mild soap and water and patted dry with a soft towel followed by application of REJUVA-A® with a gentle rubbing motion using the fingertips. Hands should be washed after application.

It is recommended to start the therapy by applying one pea-size amount to the forehead and spread it evenly over the entire face. After tolerance to the medication is established, the dose may be doubled by applying a pea-size amount to each temple. For those patients who experience excessive irritation or discomfort, the frequency of application should be decreased to every other night or even every third night.

In treating thin-skinned, sensitive regions such as the neck area with tretinoin, it is recommended to apply REJUVA-A® thinly every third night, in the beginning, and then every other night as tolerance develops.

Treatment should be discontinued if a severe local inflammatory response is experienced. In cases where it has been necessary to discontinue therapy or to reduce the frequency of application, therapy may be re-instituted, when the adverse effects have ceased.

Therapeutic results will occur gradually. Nine to twelve months of therapy may be required before beneficial effects are seen. At that time frequency of application may be reduced to two or three times per week.

Missed Dose

If patients forget to take a dose of REJUVA-A®, they should be instructed to apply the next dose at the usual time. Patients should be instructed to not apply a double dose to make up for forgotten doses.

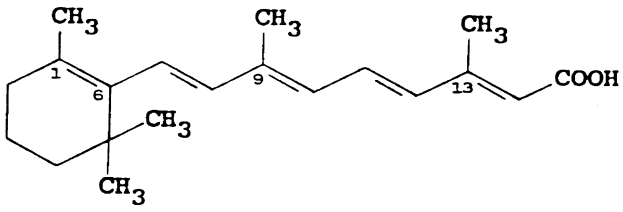
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper names: Tretinoin, retinoic acid, vitamin A acid.

Chemical name: 3,7-dimethyl-9-(2,6,6,-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-*nonatetraenoic acid.*

Structural formula:



Molecular formula: $C_{20}H_{28}O_2$ Molecular weight: 300.44

Description: Tretinoin is a yellow to light orange crystalline powder. Insoluble in water; slightly soluble in alcohol and chloroform.

Melting point: 180°C-182°C

DRUG PRODUCT

Composition: REJUVA-A® cream contains 0.025% w/w tretinoin in a moisturizing cream base with glycerine, diisopropyl adipate, stearyl alcohol, sorbitan monostearate, D.C. fluid Nos. 556 and 344, light mineral oil, polysorbate 60, carbopol 934, germaben II, butylated hydroxytoluene, sodium hydroxide as pH adjustor and purified water.

Storage: REJUVA-A® cream should be stored between 15° and 30°C. Keep out of the sight and reach of children.

AVAILABILITY OF DOSAGE FORMS

REJUVA-A® Cream: 20 g aluminium tube with fitted screw cap. Each tube contains 0.025% w/w tretinoin in a moisturizing cream base.

INFORMATION FOR THE CONSUMER

REJUVA-A® CREAM

REJUVA-A® (tretinoin cream USP 0.025% w/w): What it is, what it does and how it works.

REJUVA-A® is a tretinoin cream containing moisturizers. REJUVA-A® improves skin damaged by the sun (photo-damaged). Sun damaged skin loses elasticity. REJUVA-A® has been shown to increase the thickness and collagen level of the skin.

The tretinoin in REJUVA-A® moisturizing cream, also has an exfoliative effect which means that the skin's outer layers may peel off to leave a smoother, healthier looking surface and skin tone.

Do not use REJUVA-A® if you have an allergy to retinoids or to any of the other ingredients in REJUVA-A® or components of the container.

It is important to understand that your doctor has given you a prescription specially suited to your particular needs and skin type. **Do not allow others to use it.** Applying too much REJUVA-A® or applying it more frequently may irritate your skin and is unlikely to speed up treatment.

Following your doctor's directions carefully will minimize common reactions such as mild burning sensations and redness. Your doctor will tell you how often to apply REJUVA-A®. How often you use REJUVA-A® will depend on your individual condition and skin type.

During the first three weeks of treatment, your doctor may recommend application of REJUVA-A® on every second day to allow your skin to adjust to the medication.

Check with your doctor before using acne medication or any other skin medication as these should be used with caution when using REJUVA-A®. If you use an acne or skin medication, it should be applied at a different time of the day.

You may use water-based, noncomedogenic, hypoallergenic and oil-free cosmetics. Avoid alcohol-based lotions. Some cosmetics have a strong drying effect, such as those with a high concentration of alcohol and/or astringents, or those that have a potential irritating effect (abrasive agents, products containing spices or limes, etc.) and should be used with caution as they may irritate your skin. After applying REJUVA-A®, allow your skin to dry before applying cosmetics.

Dermatologists usually advise patients that, with regular use of topical tretinoin, clinical benefits will be obtained after six months to one year of therapy, so be patient.

Your doctor may recommend a daytime moisturizer if your skin is particularly dry.

The safety and effectiveness of REJUVA-A® in people under 18 years of age are not known and REJUVA-A® is not recommended for this population.

REJUVA-A® should not be used by pregnant women. If you are a female of childbearing age, you should only use REJUVA-A® after consulting your doctor and seeking his/her advice about the proper use of an effective method of contraception. Nursing is not recommended during treatment with REJUVA-A®. If you are pregnant, or nursing a child you should discontinue the use of REJUVA-A® and consult your doctor. There is no information on how REJUVA-A® might affect fertility.

Before you use REJUVA-A®, talk to your doctor if:

- you have a history of local tolerability reactions, photoallergy, or local hypersensitivity, or other skin conditions
- you cannot tolerate or have skin reactions to sunlight
- you have a personal or family history of skin cancer
- you have eczema, redness of the skin, broken blood vessels and tiny pimples usually on the central area of the face (rosacea), or redness and soreness around the mouth (perioral dermatitis). REJUVA-A® may further irritate these conditions

Instructions for use:

1. Wash your hands before applying the medication.
2. Wash the affected area with a mild soap and warm water and gently pat dry with a soft towel.
3. REJUVA-A® should be applied to the affected area once a day just before bedtime.
4. Your doctor will probably recommend beginning the therapy by applying one pea-size amount to the forehead and spread it evenly over the entire face. After tolerance to the medication is established, the dose may be doubled by applying a pea-size amount to each temple.
5. Use your fingertips to spread the medication over your entire face and smooth in with a gentle rubbing motion. Wash your hands after applying the medication.
6. Special care should be taken when treating wrinkles around the eyes (Crow's feet) and mouth. Do not apply to eyelids.
7. If you intend to treat thin-skinned, sensitive areas such as the neck region, it is recommended to develop gradually the tolerance to REJUVA-A® by applying the medication every third night in the beginning and then every other night.
8. In the morning, wash your face using a mild soap.
9. If you forget to use REJUVA-A®, apply the next dose at the usual time. Do not apply a double dose to make up for forgotten doses.

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Precautions

1. If you have skin irritation (redness, peeling or discomfort) or your skin is irritated from other treatments, this should be resolved before starting treatment with REJUVA-A®.
2. Do not use on sensitive and mucous-producing areas such as scraped, irritated, inflamed, cut or open skin, eyes, mouth, lips, nostrils, angles of the nose and corners of the eyes and mouth. Also, do not use on areas of the skin where you have other problems such as eczema. In case of accidental contact with the eyes or sensitive areas, rinse well with water. If REJUVA-A® gets into the eye, rinse well with water and contact your physician immediately. If discomfort persists, consult your physician.
3. Do not over-apply REJUVA-A®. Doing so will not improve how fast REJUVA-A® works, but may only increase the likelihood of severely irritating your skin. If sever irritation occurs, stop taking REJUVA-A® and consult your physician.
4. Tell your doctor about all other medications you are taking. Do not start new medications without consulting your doctor. Tell your doctor if you are taking any of the following medications as these may worsen the side effects of REJUVA-A®. Your doctor will determine whether these should be used with REJUVA-A®:
    - a peeling agent such as sulfur, resorcinol or salicylic acid
    - medications that make you sensitive to light such as thiazides, tetracyclines, fluroquinolones, phenothiazines, or sulphonamides
    - medications containing benzoyl peroxide.
5. At the beginning, you may experience redness, a burning sensation, and peeling of the skin while your skin adjusts to the medication or you may experience skin irritation (redness, peeling or discomfort). To deal with this, your doctor may reduce the number of times you apply the medication.
6. Do not use too much REJUVA-A® on sensitive skin such as the neck, or allow it to accumulate in folds of your skin, including those between the nose and lips.
7. Exposure to sunlight, sunlamps, wind and cold should be avoided or minimized during treatment because REJUVA-A® heightens the susceptibility of your skin to the adverse effects of the sun. Use of broad spectrum sunscreen with a sun protection factor (SPF) of at least 15 and protective clothing over the treated areas is recommended when exposure cannot be avoided. The sunscreen should be re-applied each time you have been swimming.
8. If you have sunburn, allow the sunburn to settle before starting treatment with REJUVA-A®. If sunburn occurs while using REJUVA-A®, stop using REJUVA-A® and call your doctor for advice.
9. Avoid or minimize exposure to weather extremes such as wind or cold as this may irritate your skin while using REJUVA-A®.
10. Following skin procedures such as depilation, chemical hair treatments, chemical peels, dermabrasion or laser resurfacing, allow the skin to recover before starting treatment with REJUVA-A®.
11. REJUVA-A® has been prescribed for your use only. Do not allow others to use it.

Side Effects

During the first weeks of using REJUVA-A®, you may notice some skin irritation such as redness and skin flaking. These symptoms will normally subside if you use REJUVA-A® less often or stop using it for a few days and then start again.

Other side effects that have been reported are: skin pain, itching/itchy skin, skin irritation, tenderness, warm skin, especially when first applied, stinging or burning sensation, dry skin, swelling at the site of application, rash at the site of application, redness at the site of application, skin blistering, skin crusting, allergic reaction, darkening of skin, lightening of skin, sensitivity to sunlight and skin thinning. Talk to your doctor if any of the side effects become severe or troublesome.

Severe skin reactions (severe burning, peeling or itching of your skin) have also been reported. Stop taking REJUVA-A® and contact your doctor immediately if you get any of these symptoms.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you accidentally swallow REJUVA-A®, seek medical advice.

Storing your medicine

Store between 15° and 30°C. Keep out of the reach and sight of children.

PHARMACOLOGY

Tretinoin is a known metabolite of vitamin A. It appears to form oxidation products that are excreted in the urine and glucuronides excreted in the feces.

In human cutaneous absorption of retinoic acid was studied by application of 3 grams of ^{14}C labelled 0.1% retinoic acid cream on 200 cm^2 of skin. After administration, radioactivity was detected in samples of blood, urine, stool and on skin occlusive dressings.

In subjects pre-treated with unlabelled material, slight increases in their blood radio-activity were observed 8 hours after application of the labeled material. In patients not pre-treated, no significant increases in radio-activity were observed.

Urine recovery studies in the subjects not pre-treated showed a 1.24 to 2.60% (mean: 1.82%) urinary excretion of the applied dose. The mean urinary excretion of the pre-treated subjects was 4.45%. Between 0.3 and 2.89% (mean: 1.58%) of the material was recovered in the stool of the pre-treated subjects. Extraction of radio-activity from skin occlusive dressings accounted for 73 to 96% (mean: 85.9%) of the applied dose.

In a further study, two and four hours after application of radio-actively labeled tretinoin to normal human skin, tretinoin was minimally detectable in the horny layer and sebaceous glands, but appreciably higher levels were found in the hair follicles and apocrine glands. After 24 hours, no penetration of radioactivity was detected beyond the Malpighian layer.

Clinical evaluation of the photosensitivity potential of topical STIEVA-A® cream (0.3%, 0.1% and 0.05%) in one short-term study has shown the preparation to be free of phototoxic properties.

Relatively large systemic doses of tretinoin produced minor changes in the circulatory system of the cat. With 100 mg/kg, reduced perfusion in the hind extremities was noted, but there was no influence on blood pressure or respiration. Using 250 mg/kg, a mild reduction in blood pressure and a slight increase in pulse rate and circulation in the hind extremities were apparent. At a higher dose (1000 mg/kg), a pronounced increase in blood pressure and irregular respiration were observed; cardiac arrest followed fifteen minutes later.

Tretinoin, when administered orally or intraperitoneally, was shown to have a therapeutic effect on chemically induced skin papillomas and skin carcinomas in mice. The extent of the regression of the papillomas appeared to be dependent on the dose and duration of treatment. Tretinoin was also shown to have not only a prophylactic effect on the induction of papillomas but on the development of carcinomas in mice. It has been observed in mice, that tretinoin applied to experimentally produced dermatologic wounds, stimulated wound healing.

The effect of tretinoin on the survival of skin grafts in mice has been investigated. Tretinoin is thought to increase the susceptibility of skin homographs to the process of immunological rejection.

In several studies, tretinoin was administered orally to rats. It appears that little, if any, free tretinoin could be detected in the bile. Retinoyl ß-glucuronide is apparently the only naturally occurring metabolite in rat bile. The glucuronide undergoes ester interchange or dehydration reactions which result in the formation of all trans- or cis-methyl retinoates and retinoyl ß-glucurono-g-lactone, respectively. Retinoyl ß-glucuronide was also identified in the liver and intestine.

TOXICOLOGY

TABLE I - Acute Toxicity

	LD_{50} (mg/kg*)			
Species	Tretinoin Pure Substance		0.1% and 0.3% Cream Formulation	0.05% Solution
	p.o.	i.p.	p.o.	p.o.
Mice	2580	791	>40 (0.1%) >60 (0.3%)	9.5±0
Neonatal Rats	225±14	--	--	--
Rats	1995	786	>60 (0.3%)	13±1
Rabbits	--	--		>5
* As active ingredient				

In the animals receiving the 0.05% solution, decreased motor activity, hypnosis, salivation and vasodilation occurred. Tretinoin pure substance suspended in 5% gum acacia produced sedation, respiratory depression, diarrhea and alopecia in mice and rats. In neonatal rats receiving the pure substance, cyanosis and stunted growth were noted.

In a dog tolerance study, tretinoin pure substance was tolerated at an oral dose of 320 mg/kg. A single oral dose of 10 mL/kg of the cream formulation (0.3%) produced emesis and an elevation of SGOT and SGPT levels.

In another dog tolerance study, 2 mL/kg of the solution formulation produced emesis and the polymorphonuclear leucocyte/lymphocyte ratio increased in one dog.

Subacute toxicity

Tretinoin was administered orally to rats at levels of 0.78, 1.56, 3.12, 6.25 and 12.5 mg/kg per day for eleven days. All the high dose animals died within five days and one animal from each of the next three lower dose groups died during the study, while all animals survived at the lowest dose level. Intestinal irritation and diarrhea were noted. Skeletal fractures were observed in several animals.

In a four-week oral study in rats (2.5, 5, 10 and 20 mg/kg tretinoin per day), body weight gain was poor in the 20 mg/kg dose group. No bone fractures were observed in this study.

In a subsequent nine-week study in rats, tretinoin was administered orally at 1.56 and 3.12 mg/kg per day levels and no mortality occurred. Females had a slight increase in body weight gain and the males showed a slight decrease.

Four groups of rats received topical applications of a 0.3% cream at levels corresponding to 0, 1.5, 3 and 6 mg/kg/day of tretinoin five days per week for thirteen weeks. Food consumption and body weight gain were slightly reduced in the high dose group. Skin lesions with irritation and inflammation were noted and appeared to be dose dependent. Elevated total and polymorphonuclear leucocyte counts were observed in all dose groups. With the exception of a 3 mm mammary tumor in a control animal, there were no gross changes observed at autopsy. Microscopy examination of the skin revealed focal ulcerations and inflammatory changes of significant degree in the high and mid dose groups.

In another thirteen-week rat study, 6 mg/kg of tretinoin per day administered seven days per week in the diet was well tolerated although body weight gain, red blood cell count, packed cell volume, hemoglobin concentration and serum protein values all decreased.

On the other hand, plasma alkaline phosphatase values were markedly elevated. Histological examination revealed hyperplasia of blood-forming elements, increase in number and size of Kupffer liver cells, hydropic changes in the protoplasm of hepatocytes, increased number of foam cells and lymphatic elements of the lung, thinning of the epidermis and proliferation around the hair follicles.

In a thirteen-week dog study, tretinoin was administered orally to four groups of dogs at levels of 0, 3, 10 and 30 mg/kg per day seven days per week. No mortality occurred in any of the groups. In the high dose group, one dog lost about 25% of his initial body weight. Eczema, acanthotic proliferation of the epidermis and diarrhea were also noted in the 10 and 30 mg/kg groups. Low erythrocyte count, hemoglobin concentration on and packed cell volume were noted in the 30 mg/kg group. Changes in the albumin and gamma globulin fractions were seen and blood sedimentation rates increased in the two highest dose groups. Lack of spermatogenesis and atrophy of the tubular epithelia occurred; there was hyperplasia of the blood-forming elements in bone marrow in the high dose group.

Topical applications

Eye and skin irritation studies were performed on rabbits with the tretinoin cream formulation at concentrations ranging from 0.01% to 0.5%. In the eye irritation test, slight reddening of the conjunctiva occurred. Very slight edema and well defined to moderate erythema were produced when applied to abraded and un-abraded rabbit skin. In subsequent irritation studies in rabbits, tretinoin, a 0.3% cream and a placebo cream were compared. The same degree of irritation was noted in the three groups. Tretinoin substance produced slight erythema, while the cream and placebo produced well-defined erythema and slight edema to rabbit skin.

In another study, the 0.05% tretinoin solution and a placebo were tested in rabbits. There appeared to be a very slight reddening of the conjunctiva and a very slight discharge with both placebo and test solution groups. The placebo and test solution were considered non-irritating to the skin.

Teratology

Female mice received tretinoin in oral doses of 1, 3, 9, 17, 43, 86 and 130 mg/kg from the 9th to 10th day of gestation. A slight increase in the incidence of skeletal malformations was observed in the low dose group (1 mg/kg). A pronounced teratogenic effect was produced with 3 mg/kg and higher doses. Multiple malformations of the head (cleft palate, exencephaly) were observed most frequently.

A slight increase in rate of resorption occurred at 3 mg/kg. With 9 mg/kg, 50% of all implanted embryos were resorbed. At still higher doses, complete resorption occurred.
In a study in which 10 mg/kg per day was administered by gavage to 11 pregnant monkeys from days 20 to 45 of gestation several teratogenic defects were observed. Specific defects such as cleft palate, auricular malformation, open eye with unilateral ablepharia, kyphosis, scoliosis, missing digits and severe curvature of the radius were observed. Vaginal hemorrhage was observed frequently in the mothers. Abortion or fetal death with intrauterine retention (in 6 of the 11 mothers) was also observed. Three normal fetuses resulted, two of which aborted before term.

In one study no teratogenic effects were seen in the fetuses when Vitamin A acid was topically applied daily to the skin of pregnant rats during the second third of gestation.

Results from topical teratology studies in rats and rabbits have been inconclusive.

Carcinogenesis and Mutagenesis

Carcinogenic studies have not been conducted with REJUVA-A®. Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of ultra violet radiation.

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