PRODUCT MONOGRAPH

PrSTIEVA-A®

Tretinoin gel, USP, 0.025%, 0.05% w/w

Tretinoin cream, USP, 0.01%, 0.025%, 0.05%, 0.1% w/w

Topical Acne Therapy

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

Date of Revision:
October 20, 2011

Control Number: 148469

PRODUCT MONOGRAPH

PrSTIEVA-A®
Tretinoin gel, USP, 0.025%, 0.05% w/w

Tretinoin cream, USP, 0.01%, 0.025%, 0.05%, 0.1% w/w

THERAPEUTIC CLASSIFICATION

Topical Acne Therapy

ACTION AND CLINICAL PHARMACOLOGY

The precise mechanism of action of tretinoin on the skin is not fully understood. It is known that tretinoin is both pharmacologically and structurally related to vitamin A which regulates epithelial cell growth and differentiation. Tretinoin itself is known to have an irritant and keratolytic effect on the skin. These two actions which occur simultaneously have been shown histologically in both animal and man to be associated with an increased growth rate and with a decrease in the cohesiveness of the epidermal cells. The result is a slightly thickened epidermis with an accelerated turnover rate and shedding of keratinized cells as very fine barely perceptible scales.

In acne vulgaris the induced fine scaling of the skin surface is accompanied by an increased production of less cohesive epidermal sebaceous cells, which consequently flow out of the follicle at a more rapid rate. The thickened mass of sebaceous cellular debris, the comedones appear to be initially extruded and then prevented from recurring by these actions[3]. Histopathologically, acne is the impaction plus distension of the sebaceous follicles by tightly packed horny cells and disruption of the follicular epithelium. It has been postulated that tretinoin inhibits the synthesis or quality of the substance which binds the horny cells within the sebaceous follicle.

INDICATIONS AND CLINICAL USE

STIEVA-A® (tretinoin 0.01%, 0.025%, 0.05%, or 0.1% w/w) is indicated in the treatment of acne vulgaris, primarily where comedones, papules and pustules predominate. STIEVA-A® is not effective in most cases of severe pustular and deep cystic nodular varieties (acne conglobata).

Geriatrics (> 65 years of age): Safety and effectiveness of STIEVA-A® in patients aged 65 years and above have not been established.

Pediatrics (< 12 years of age): Safety and effectiveness of STIEVA-A® in patients below the age of 12 years have not been established.

CONTRAINDICATIONS

STIEVA-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 Composition and Availability of Dosage Forms.

WARNINGS

STIEVA-A® IS INTENDED FOR EXTERNAL USE ONLY AND SHOULD BE KEPT AWAY FROM ABRADED SKIN, LIPS, EYES, NOSE, MOUTH, 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.

Do not apply to eyelids or to the skin at the corners of the eyes and mouth. Avoid the angles of the nose, skin fold areas and nasolabial fold (if treatment in these areas is necessary, apply very sparingly).

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.

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

STIEVA-A® has been reported to cause severe irritation of eczematous skin and should only be used with utmost caution in patients with this condition.

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 (< 12 years of age)

Safety and effectiveness in patients below the age of 12 years have not been established, therefore the STIEVA-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.

STIEVA-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.
- inflammatory skin conditions that coexist with acne.
- sensitive skin and/or fair complexion.

During early weeks of therapy, an apparent exacerbation of the acne lesions may occur due to an expected drug effect on previously unseen deep lesion. This is an anticipated therapeutic effect and therapy should be continued. Dosing frequency may be reduced or a lower strength of STIEVA-A® may be used, if applicable, to help prevent exacerbation of acne lesions.

STIEVA-A® Gel is flammable. Avoid open flame or smoking during and immediately following application.

Skin

Due to the irritant nature of tretinoin, caution should be used when applying to sensitive areas of skin, such as the neck, or in patients with inflammatory skin conditions that coexist with acne.

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

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

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

Due to the potential for photosensitivity, resulting in a greater risk for sunburn, STIEVA-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 STIEVA-A®. If sunburn occurs while using STIEVA-A®, it is advisable to interrupt therapy until the severe erythema and peeling subside.

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

Carcinogenesis and Mutagenesis

Carcinogenicity studies with STIEVA-A® have not been conducted. Studies in hairless mice suggest that concurrent dermal exposure to isotretinoin, an isomer of tretinoin, may enhance the tumorigenic potential of ultraviolet irradiation.

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 (e.g., one in the morning and the other in the evening).

Augmented Photosensitivity

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

Cumulative Irritation

Concomitant topical acne therapy and other topical medications should be used with caution 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 STIEVA-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 STIEVA-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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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%).

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 oedema/swelling, skin atrophy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, 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.

The highest strength formulation of STIEVA-A® contains 0.1% tretinoin. Therefore, a 45 g tube would contain 45 mg tretinoin.

In case of a suspected overdosage, a symptomatic and supportive treatment should be instituted. Inadvertent oral ingestion of STIEVA-A® gel or 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.

Topical gel contains more than 95% ethanol. Systemic absorption of this should be considered in the event of oral ingestion.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dose Adjustment

STIEVA-A® should be applied sparingly to the affected area once a day before bedtime for up to 12 weeks.

Therapeutic results may be noticed after two to three weeks of therapy; however, results may not be optimal until after eight to ten weeks of treatment. Once the

acne lesions have responded satisfactorily, it may be possible to maintain the improved state with less frequent applications; however a maintenance dose has not been studied or established.

Excessive application will not improve efficacy, but may increase the risk of severe irritation.

The efficacy and safety of STIEVA-A® has not been studied beyond 12 weeks in acne vulgaris clinical trials.

During the first three weeks of treatment, STIEVA-A® may be applied every second day to allow the patient's skin to adjust to the medication, especially for patients with sensitive skin and/or a fair complexion.

Formulation strength should be selected and adjusted according to the patient's tolerance.

In case of an apparent exacerbation of the acne lesions during early weeks of therapy, dosing frequency may be reduced or a lower strength of STIEVA-A® may be used (see PRECAUTIONS).

Concomitant medicated and non-medicated therapies should be used with caution (see DRUG INTERACTIONS).

In cases of undue skin irritation (redness, peeling, or discomfort), the frequency of application should be reduced (e.g., application every other day), use a lower strength of the product, if applicable, or temporarily interrupt treatment. The normal frequency of application should be resumed once the skin irritation subsides. Treatment should be discontinued if skin irritation persists.

Because of increased sensitivity of ultraviolet radiation associated with the use of tretinoin, patients should be instructed to use a broad spectrum sunscreen with an SPF of at least 15, to re-apply sunscreen regularly and to wear protective clothing (see PRECAUTIONS).

Administration

The area under treatment (not just clinical lesions) should be thoroughly cleansed with a mild soap, and dried, followed by application of STIEVA-A® with a gentle application. Hands should be washed before and after application. Application may be accompanied by a transitory feeling of warmth or a stinging sensation. Patients may also use a moisturiser as needed.

Do not apply STIEVA-A® to eyelids or to the skin at the corners of the eyes and mouth. Avoid the angles of the nose, skin fold areas and nasolabial fold. If treatment in these areas is necessary, apply very sparingly. Caution should be used when applying to sensitive areas of skin, such as the neck, or in patients with inflammatory skin conditions that coexist with acne (see WARNINGS).

Patients being treated with STIEVA-A® may continue to use water-based, noncomedogenic, hypoallergenic and oil-free cosmetics. Following application of STIEVA-A®, the patient should be instructed to allow the skin to dry before applying cosmetics (see DRUG INTERACTIONS).

If combination therapy is required, consideration should be given to applying the products at different times of the day (e.g. one in the morning and the other in the evening (see DRUG INTERACTIONS).

Missed Dose

If patients forget to take a dose of STIEVA-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.

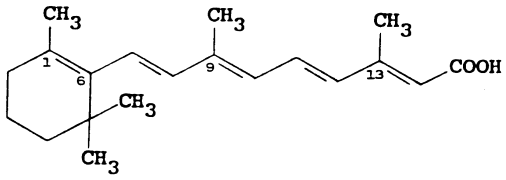
PHARMACEUTICAL INFORMATION

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: $C_{20}H_{28}0_2$ 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: **STIEVA-A® Gel** contains 0.025% or 0.05% tretinoin in a vehicle gel of butylated hydroxytoluene and hydroxypropyl cellulose and denatured alcohol.

STIEVA-A® Cream contains 0.01%, 0.025%, 0.05% or 0.1% (Forte) tretinoin in a cream base of polyoxyl 40 stearate, stearyl alcohol, stearic acid, isopropyl palmitate, white petrolatum, butylatedhydroxytoluene,butylated hydroxyanisole, propyl and methyl parabens ethylenediaminetetraacetic acid disodium salt, propylene glycol and purified water; and titanium dioxide in the 0.1% (Forte) tretinoin cream.

Stability & Storage

Recommendations: Store between 15º C and 30° C. Keep the tube tightly closed when not in use.

AVAILABILITY OF DOSAGE FORMS

STIEVA-A® Cream: 45 g aluminum tubes with polypropylene caps. Each tube contains tretinoin, in strengths of 0.01%, 0.025%, 0.05%, or 0.1% (Forte), in a cream base.

STIEVA-A® Gel: 45 g aluminum tubes with polypropylene caps. Each tube contains tretinoin, in strengths of 0.025% or 0.05%, in an alcohol base gel.

INFORMATION FOR THE CONSUMER

STIEVA-A® Cream, Gel

STIEVA-A® (tretinoin 0.01%, 0.025%, 0.05%, or 0.1% w/w): what it is, what it does, and how it works

STIEVA-A® is a cream or gel containing a drug dermatologists have long prescribed in the treatment of acne.

It works by penetrating deeply into the skin to unplug pores, and then aiding the natural flow and elimination of excess oils from the sebaceous glands.

In addition, STIEVA-A® has an exfoliative effect, which means the skin's outer layers may peel off to leave a smoother, healthier-looking surface and skin tone.

After many years of experience with tretinoin, dermatologists usually advise patients that with regular use of STIEVA-A®, visible improvement should be seen in 6-8 weeks, so be patient.

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.** Also, over-application of STIEVA-A® 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.

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

Use of any other acne or skin medication should be discontinued when using STIEVA-A® unless your physician advises otherwise.

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 STIEVA-A®, allow your skin to dry before applying cosmetics.

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

STIEVA-A® should not be used by pregnant women. If you are a female of child bearing age, you should only use STIEVA-A® after consulting your doctor and seeking his/her advice about the proper use of an effective method of contraception. If you are pregnant or nursing a child you should discontinue the use of STIEVA-A® and consult your doctor.

Talk to your doctor if you have a history of local tolerability reactions, photoallergy, or local hypersensitivity, a personal or family history of skin cancer, other skin conditions, or sensitive and/or fair complexion.

Instructions for use

1. Wash your hands before applying the medication.
2. Wash affected area with a mild soap and warm water and gently dry. Wait 20-30 minutes for the face to fully dry.
3. Apply STIEVA-A® sparingly and evenly once daily, preferably before bedtime. Use your finger-tip to apply enough to cover the required area, and smooth in. Wash your hands after applying the medication.
4. Avoid sensitive areas such as irritated skin, mouth, eyes, lips, nostrils and mucous-producing areas. Also avoid areas of skin where you have other problems, such as eczema. In case of accidental contact, rinse well with water. If discomfort persists, consult your physician. If STIEVA-A® gets into the eye, rinse well with water and contact your physician immediately.
5. In the morning, wash your face using a mild soap.
6. If you forget to use STIEVA-A®, apply the next dose at the usual time. Do not apply a double dose to make up for forgotten doses.

Precautions

1. **FLAMMABLE:** Avoid open flame or smoking during and immediately following application. Keep away from heat sources and keep tube tightly closed when not in use.
2. Do not apply STIEVA-A® to areas of skin where you have problems such as eczema, severely inflamed skin or other open lesions.
3. If you have skin irritation (redness, peeling or discomfort) or your skin is irritated from other treatments, including those used for your acne, this should be resolved before starting treatment with STIEVA-A®.
4. Avoid sensitive and mucous-producing areas such as scraped, cut or open skin, eyes, mouth, lips, angles of nose, and corners of eyes and mouth.

5. Do not over-apply STIEVA-A®. Doing so will not improve how fast STIEVA-A® works, but may only increase the likelihood of severely irritating your skin. If severe irritation occurs, stop taking STIEVA-A® and consult your physician.
6. Tell your doctor about all other medications you are taking. Do not start new medications without consulting your doctor.
7. 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 or may give you a lower strength of STIEVA-A® and may gradually increase the strength of the medication you use.
8. If you have sensitive skin and/or a fair complexion, you may more likely to experience skin irritation while using STIEVA-A®.
9. At the beginning, you may experience a worsening of your acne. To help prevent this, your doctor may lower the strength, if applicable, or adjust how frequent you apply STIEVA-A®.
10. Avoid or minimize exposure to sunlight and sun lamps because STIEVA-A® heightens the susceptibility of your skin to the adverse effects of the sun.
11. Use of a broad spectrum sunscreen with a sun protection factor (SPF) of at least 15 and protective clothing over treated areas is recommended when exposure cannot be avoided.
12. If you have sunburn, allow the sunburn to settle before starting treatment with STIEVA-A®. If sunburn occurs while using STIEVA-A®, stop using STIEVA-A® and call your doctor for advice.
13. Avoid or minimize exposure to weather extremes such as wind or cold as this may irritate your skin while using STIEVA-A®.
14. Following skin procedures such as depilation, chemical hair treatments, chemical peels, dermabrasion or laser resurfacing, allow the skin to recover before starting treatment with STIEVA-A®.

15. STIEVA-A® has been prescribed for your use only. Do not allow anyone else to use it.

Side Effects

During the first weeks of using STIEVA-A®, you may notice some skin irritation such as redness and skin flaking. These symptoms will normally subside if you use STIEVA-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 STIEVA-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.

STIEVA-A® Gel contains 95% ethanol; in case of accidental oral ingestion, this should be taken into consideration and the medical personnel informed.

Storing your medicine

Store between 15° and 30°C. Keep the tube tightly closed when not in use.

PHARMACOLOGY

Tretinoin is a known metabolite of vitamin A. It appears to form oxidation products which 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, radio-activity 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 labelled 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, 2 and 4 hours after application of radio-actively labelled 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 radio-activity 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

Acute Toxicity

LD_{50} (mg/kg*)				
	Tretinoin		0.1% and 0.3%	0.05%
	Pure Substance		Cream Formulation	Solution
Species	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	-	-	>60 (0.3%)	>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 AST (SGOT) and ALT (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 or 12.5 mg/kg/day for 11 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 animal.

In a four-week oral study in rats (2.5, 5, 10 or 20 mg/kg tretinoin per day), body weight gain was poor in the 20 mg/kg/day 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/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 or 6 mg/kg/day of tretinoin 5 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. Microscopic 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 7 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 dose levels of 0, 3, 10 or 30 mg/kg/day 7 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 unabraded 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 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 or 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/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[6]. 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

Carcinogenicity studies with STIEVA-A® have not been conducted. Studies in hairless mice suggest that concurrent dermal exposure to isotretinoin, an isomer of tretinoin, may enhance the tumorigenic potential of ultraviolet irradiation.

BIBLIOGRAPHY

1. Vitamin A deficiency and xenophthalmia. World Health Organization Technical Report 1976; Series No. 590: 11-16

2. Frost P, Weinstein GD, Topical administration of vitamin A for ichthyosiform dermatosed and psoriasis. JAMA 1969; 207: 1963 - 1968.

3. Klingman AM, Fulton JE, Plewig G. Topical vitamin A acid in acne vulgaris. Arch Derm 1969; 99:469-476.

4. Leyden JJ, Kligman AM. Acne vulgaris: New concepts in pathogenesis and treatment. Drugs 1976; 12: 292-300.

5. De Luca HF, Roberts AB. Pathways of retinoic acid and retinol metabolism. AM J Clin Nutr 1969; 22: 945-952.

6. Fantel AG, Shepard TH, Newell LL, Moffett BC. Teratogenic effects of retinoic acid in monkeys. Teratology 1975; 11: 17A.

7. Herold M, Cahn J, Gamont P. Toxicology of vitamin A acid. Acta Dermato Venerol 1975; 55: 29-32.

8. Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. The Lancet 1993; 341: 1181-1182.