# PRODUCT MONOGRAPH

**STIEVA-A® Gel**
(Tretinoin Gel USP)

**STIEVA-A® Cream**
(Tretinoin Cream USP)

**STIEVA-A® Solution**
(Tretinoin Topical Solution USP)

## Topical Acne Therapy

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**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) 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).

## CONTRAINDICATIONS

STIEVA-A® (tretinoin) is contraindicated in patients with known hypersensitivity to retinoids or to any ingredient contained in the preparation.

## WARNINGS

**STIEVA-A® IS INTENDED FOR EXTERNAL USE ONLY AND SHOULD BE KEPT AWAY FROM EYES, NOSE, MOUTH, AND OTHER MUCOUS MEMBRANES BECAUSE OF ITS IRRITANT EFFECT.**

Do not apply to eyelids or to the skin at the corners of the eyes and mouth. Avoid the angles of the nose 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® (tretinoin) has been reported to cause severe irritation of eczematous skin and should only 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 reports of birth defects among babies born to women exposed to topical tretinoin during pregnancy. However, there are no well-controlled prospective studies of the use of topical tretinoin in pregnant women. A retrospective study of mothers exposed to topical tretinoin during the first trimester of pregnancy found no increase in the incidence of birth defects.

Topical retinoid teratology studies in rats and rabbits have been inconclusive. As with all retinoids, tretinoin administered orally at high doses is teratogenic.

**Use in 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.**

## PRECAUTIONS

Concomitant topical medications should be used with caution during therapy with STIEVA-A® (tretinoin) because of possible intensified reactions. Particular caution should be exercised when using preparations containing a peeling agent concomitantly

(such as sulfur, resorcinol, benzoyl peroxide or salicylic acid) with STIEVA-A®. It may be advisable to "rest" a patient's skin until the effects of previously used peeling agents subside before initiating STIEVA-A® therapy.

Exposure to sunlight and sun lamps should be avoided or minimized during the use of STIEVA-A® because of heightened susceptibility to UV radiation as a result of the use of tretinoin.

If a sunburn occurs, it is advisable to interrupt therapy until the severe erythema and peeling subside. Patients whose occupations require considerable exposure 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.

## ADVERSE REACTIONS

The skin of certain sensitive individuals, particularly those with fair complexion, may become excessively red, edematous, blistered or crusted when exposed to STIEVA-A®. Pain, burning sensation, tenderness, irritation or pruritus have also been occasionally reported. 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. Temporary hyper- or hypo-pigmentation has been reported with repeated application of tretinoin. To date, all adverse clinical effects of STIEVA-A® encountered have been reversible upon discontinuance of therapy. In many instances, reinstitution of therapy with STIEVA-A® failed to produce the adverse effect previously experienced.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Topical: If medication is applied excessively, marked redness, peeling or discomfort may occur.

Inadvertent oral ingestion of STIEVA-A® gel, cream or solution 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

STIEVA-A® should be applied to the affected area once a day before retiring. The area under treatment (not just clinical lesions) should be thoroughly cleansed with a mild soap, such as Acne-Aid Soap, and dried, followed by application of STIEVA-A® with a gentle rubbing motion. Application may be accompanied by a transitory feeling of warmth or a stinging sensation. 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 applications, therapy may be resumed, when the adverse effects have ceased. In some patients, during the early weeks of therapy, an apparent exacerbation of the acne lesions may occur.

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.

Patients being treated with STIEVA-A® may continue to use cosmetics; however, the area of skin to be treated should be thoroughly cleansed and dried before STIEVA-A® application.

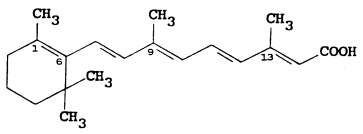
## PHARMACEUTICAL INFORMATION

### 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.

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% tretinoin in a vanishing 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% tretinoin cream.

**STIEVA-A® Solution** contains 0.025% tretinoin in a solution of butylated hydroxytoluene, hydroxypropyl cellulose, purified water and denatured alcohol.

Stability & Storage Recommendations: STIEVA-A® Creams, Gels and Solutions should be stored between 15°C and 30°C.

## AVAILABILITY OF DOSAGE FORMS

STIEVA-A® Cream: 25 g and 45 g tube containing 0.01%, 0.025%, 0.05% or 0.1% tretinoin in a vanishing cream base.

STIEVA-A® Solution: 50 mL bottles containing 0.025% tretinoin in an alcohol solution.

STIEVA-A® Gel: 25 g and 45 g tube containing 0.025% or 0.05% tretinoin in an alcohol base gel.

## INFORMATION FOR THE CONSUMER

(PATIENT PACKAGE INSERT)

STIEVA-A®*, Creams, Gels, Solutions

### STIEVA-A®* (tretinoin): what it is, what it does, and how it works

STIEVA-A® (tretinoin) is a cream, gel or solution 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 STIEVA-A®, 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.

It is best to use only water-based cosmetics and avoid alcohol-based lotions.
Your doctor may recommend a daytime moisturizer if your skin is particularly dry.

**If you are a female of child bearing age, you should only use STIEVA-A® after consulting your doctor and seeking his/her advice for contraceptive counselling. If you are pregnant, you should discontinue the use of STIEVA-A® and consult your doctor.**

**Instructions for use**

1. Wash affected area with a mild soap and warm water and gently dry. Wait 20-30 minutes for the face to fully dry.
2. 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.
3. Avoid sensitive areas such as eyes, lips and mucous-producing areas. Also avoid areas of skin where you have other problems, such as eczema.
4. In the morning, wash your face using a mild soap.
5. At the beginning, you may experience redness, a burning sensation, and peeling while your skin adjusts to the medication which flushes existing oil and debris out of your pores.
6. To minimize these reactions, your doctor may start you on the mildest strength of STIEVA-A® 0.01% and go up gradually until you reach the strength that your doctor feels is most suitable for your skin type.
7. Since STIEVA-A® works from beneath the skin's surface, it takes several weeks of regular use before you can expect noticeable improvement.

**Precautions**

1. Do not apply STIEVA-A® to areas of skin where you have problems such as eczema, severely inflamed skin or other open lesions.
2. Avoid sensitive and mucous-producing areas such as eyes, mouth, lips, angles of nose, and corners of eyes and mouth.
3. Do not over-apply STIEVA-A®. Doing so will not speed up treatment, but only irritate your skin.
4. While using STIEVA-A®, do not use other acne or skin medications without the advice of your physician.
5. 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.
6. 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.
7. If sunburn occurs, stop using STIEVA-A® and call your doctor for advice.
8. Your doctor has given you STIEVA-A® for your use only. Do not allow anyone else to use it.

## PHARMACOLOGY

Tretinoin is a known metabolite of vitamin A. It appears to form inactive 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 STIEVA-A® 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 Pure Substance | | 0.1% and 0.3% Cream Formulation | 0.05% Solution |
|---|---|---|---|---|
| Species | p.o. | i.p. | p.o. | p.o. |
| Mice | 2580 | 791 | >40 (0.1%)<br>>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 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 animal.

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. 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 levels of 0, 3, 10 and 30 mg/kg per 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 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[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.

## 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.