

# AUSTRALIAN PRODUCT INFORMATION

## STIEVA-A (tretinoin) cream

### 1 NAME OF THE MEDICINE

Tretinoin

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

STIEVA-A Creams 0.025%, 0.05% and 0.1% contain the active ingredient Tretinoin USP at a concentration of 0.25 mg/g, 0.5 mg/g and 1.0 mg/g.

#### Excipients with known effect

Contains methyl hydroxybenzoate and propyl hydroxybenzoate

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

### 3 PHARMACEUTICAL FORM

Cream

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

STIEVA-A is indicated for use in the treatment of acne vulgaris, in particular forms where comedones, papules and pustules predominate. STIEVA-A is not generally effective in most cases of severe pustular or nodulocystic acne.

#### 4.2 DOSE AND METHOD OF ADMINISTRATION

##### Adults and adolescents

STIEVA-A is for topical use only.

STIEVA-A should be applied once daily before retiring - to the whole area under treatment. The skin should be thoroughly cleansed and dried before application of STIEVA-A.

Therapeutic effects may not be seen until 6-8 weeks after the start of treatment. Treatment should normally be continued for three months.

Patients being treated with STIEVA-A may continue to use cosmetics.

Patients should be advised that excessive application will not improve efficacy, but may increase the risk of skin irritation.

If undue irritation (redness, peeling or discomfort) occurs, patients may use a non-comedogenic moisturiser as needed and should reduce frequency of application or temporarily interrupt treatment. The normal frequency of application should be resumed once the irritation subsides. Treatment should be discontinued if the irritation persists.

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

### **4.3 CONTRAINDICATIONS**

- Pregnancy
- Women planning a pregnancy

Patients with known hypersensitivity to any of the ingredients should not use STIEVA-A.

Tretinoin preparations have been reported to cause severe irritation of eczematous skin and should only be used with the utmost caution in patients with this condition.

STIEVA-A should not be used in patients with a personal or family history of skin cancer.

### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Tretinoin should be used with caution in patients with a history of local tolerability reactions, photoallergy, or local hypersensitivity.

Contact with the mouth, eyes, lips, other mucous membranes, or areas of broken skin should be avoided. In case of accidental contact, rinse well with water.

Care should be taken not to let the medicine accumulate in skin fold areas and in the nasolabial folds.

Due to the irritant nature of tretinoin, caution should be used when applying to sensitive areas of skin, such as the neck, abraded or eczematous skin, or when treating patients with inflammatory skin conditions that may coexist with acne e.g rosacea or perioral dermatitis.

Concomitant topical acne therapy should be used with caution because a cumulative irritant effect may occur. If irritancy or dermatitis occur, 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 treatment, chemical peels, dermabrasion or laser resurfacing, the skin should be allowed to recover before application is considered.

Cosmetics that have a strong drying effect, including products with high concentrations of alcohol and/or astringents, or that have a potential irritating effect should be used with caution as a cumulative irritant effect may occur.

#### **Sensitivity to sunlight**

As tretinoin may cause increased sensitivity to sunlight, sunlamps should not be used and deliberate or prolonged exposure to sunlight should be avoided or minimised. When exposure to strong sunlight cannot be avoided, patients should be advised to use a broad-spectrum sunscreen product (protects against UVA and UVB rays) and wear protective clothing.

If a patient has sunburn, this should be resolved before using tretinoin.

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

Studies have shown that in mice treated with tretinoin and exposed to UV light, tretinoin may speed up the appearance of tumours induced by UV light (artificial sunlight); mice treated with tretinoin but not exposed to the light did not develop tumours. The significance of these findings as related to human beings is unknown. However, the exposure of the areas treated with STIEVA-A to sunlight should be avoided or minimised. The use of sunlamps should be avoided during treatment. Patients who have considerable sunlight exposure, for reasons such as occupation, should exercise particular caution. Use of sunscreen products and protective clothing may be prudent when sunlight exposure cannot be avoided.

### **Use in pregnancy**

STIEVA-A is contraindicated (See Section 4.3 CONTRAINDICATIONS) in pregnancy or in women of childbearing potential not using an effective method of contraception properly.

If this product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

### **Use in hepatic impairment**

No dosage adjustment is necessary.

Hepatic impairment is not expected to result in systemic exposure of clinical significance. This is because negligible percutaneous absorption of tretinoin follows topical application (See Section 5.2 PHARMACOKINETIC PROPERTIES).

### **Use in renal impairment**

No dosage adjustment is necessary.

Renal impairment is not expected to result in systemic exposure of clinical significance. This is because negligible percutaneous absorption of tretinoin follows topical application (See Section 5.2 PHARMACOKINETIC PROPERTIES).

### **Use in the elderly**

There are no specific recommendations for use in the elderly.

### **Paediatric use**

The safety and efficacy of topical tretinoin in children prior to puberty have not been established, therefore tretinoin is not recommended for use in this population.

### **Effects on laboratory tests**

No data available.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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).

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

There are no data on the effect of topical tretinoin on fertility in humans, but isotretinoin, an isomer of tretinoin, in oral therapeutic dosages does not affect the number, motility, and morphology of sperm.

Effects on fertility have not been investigated in adequate studies in animals. Minimal to marked testicular degeneration was observed in a 6-week toxicology study in dogs with oral treatment at  $\geq 2$  mg/kg/day.

### **Use in pregnancy**

#### **(Pregnancy Category D)**

Tretinoin has been shown to be teratogenic in rats following topical dermal administration of a 10 mg/kg dose given twice on a single day of gestation. Teratogenicity is also seen in mice and rats at high oral doses. Topical tretinoin has not been shown to be teratogenic in rats and rabbits when given at doses of 0.5 mg/kg/day and 1.6 mg/kg/day, respectively. However, at these topical doses, delayed ossification occurred in a number of bones in both species. These latter changes may be considered variants of normal development and are usually corrected after weaning. Foetal weight was reduced in rats with topical dermal administration at 5 mg/kg/day.

STIEVA-A is contraindicated (See Section 4.3 CONTRAINDICATIONS) in pregnancy or in women of childbearing potential not using an effective method of contraception properly.

If this product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

A number of observational studies of varying sample size involving a total of 1535 women exposed to topical tretinoin in early pregnancy did not provide evidence of an increased risk of congenital abnormalities, including retinoic acid embryopathy or major structural defects overall.

A small number of temporally associated congenital abnormalities have been reported during clinical use of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, they include reports of the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these reports in terms of risk to the foetus is uncertain, since these effects have not been reproduced.

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, there is low systemic absorption from topically administered tretinoin. However, risk cannot be excluded since there may be other factors that contribute to an increased systemic exposure such as: amount used; skin barrier integrity; concurrent use with other products; dietary intake of or ingestion of supplements containing vitamin A.

No specific contraceptive precautions are necessary for men using topical tretinoin.

## Use in lactation

There is insufficient information on the excretion of topically applied tretinoin in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue /abstain from tretinoin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following convention is used for the classification of the frequency of an adverse reaction and is based on the CIOMS guidelines:

Very common:	≥1/10
Common:	≥1/100 to <1/10
Uncommon:	≥1/1000 to <1/100
Rare:	≥1/10000 to <1/1000
Very rare:	<1/10000
Not known*:	(Cannot be estimated from the available data)

### Clinical trial data

#### ***Skin and subcutaneous tissue disorders***

Very common: Application site erythema, skin exfoliation, pain of skin, application site pruritus, skin irritation, skin tenderness, skin burning sensation, application site stinging, dry skin

The above adverse events, seen more frequently with the higher strength 0.1% cream, are generally moderate and usually subside with continued treatment.

### Post-marketing data

Skin and subcutaneous tissue disorders

Rare: skin hyperpigmentation, skin hypopigmentation, photosensitivity reaction, application site rash, application site oedema/swelling, allergic reaction, skin atrophy

## Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

### Symptoms and signs

Oral ingestion of a 30 g tube of topical tretinoin would result in less exposure than achieved with the recommended dosage of oral tretinoin. Consequently, the theoretical occurrence of symptoms of overdosage (e.g. hypervitaminosis A) is highly unlikely.

### Treatment

Appropriate symptomatic measures should be taken to provide relief from irritation due to excessive topical application.

Accidental ingestion should be managed clinically.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of action

Tretinoin is a known metabolite of vitamin A, which regulates epithelial cell growth and differentiation. It is thought that topically applied tretinoin in acne acts by:

- stimulating mitosis in the epidermis
- reducing intercellular cohesion in the stratum corneum
- contesting the hyperkeratosis characteristic of acne vulgaris
- aiding desquamation, preventing the formation of lesions
- mediating an increased production of less cohesive epidermal sebaceous cells, which appears to promote the initial expulsion of comedones and their subsequent prevention.

Tretinoin shows weak inhibition of leukotriene-B4-induced migration of polymorphonuclear leukocytes which may contribute to its topical anti-inflammatory activity. More marked inhibition of polymorphonuclear leukocyte migration is seen with isotretinoin. The weaker effect of tretinoin compared to isotretinoin may account for the greater rebound effect seen with topical tretinoin when compared with topical isotretinoin.

The pharmacological action of tretinoin remains to be fully elucidated. It has the following actions when given systemically:

- suppresses sebaceous gland activity
- reduces sebum production
- prevents or reduces comedogenesis
- suppresses *Propionibacterium acnes*
- reduces inflammation.

#### Clinical trials

No data available.

### 5.2 PHARMACOKINETIC PROPERTIES

## **Metabolism**

Tretinoin is metabolised rapidly *in vivo*, and involves isomerisation to 9-*cis*,11-*cis* and 13-*cis*-retinoic acid (isotretinoin) and oxidation to 4-oxo and 4-hydroxy metabolites.

## **Excretion**

Metabolites are excreted as glucuronide conjugates in urine and bile.

## **5.3 PRECLINICAL SAFETY DATA**

### **Genotoxicity**

Tretinoin was negative in assays for gene mutation in bacteria (Ames test) and mammalian cells (Chinese hamster lung cells). A two-fold increase in sister chromatid exchange (SCE) frequency was found in human diploid fibroblasts, but other chromosomal aberration assays (human lymphocytes *in vitro*, mouse micronucleus test *in vivo*) did not show a clastogenic or aneuploidogenic effect.

### **Carcinogenicity**

In a 91-week dermal study in mice, treatment at 0.5 and 1 mg/kg for three days per week was associated with the development of squamous cell carcinomas and papillomas in females at the site of application. These skin tumours occurred in the context of severe dermal irritation; the relevance to humans is unclear. No carcinogenicity was observed at a dose of 0.025 mg/kg (less than the maximum human dose, adjusted for body surface area).

The tumourigenic potential of UV irradiation was increased with concurrent dermal exposure to tretinoin at a dose of 100 mg/kg in hairless albino mice. Although the relevance of this finding to humans is unknown, patients should minimise exposure to sunlight or artificial UV sources (see also Sensitivity to sunlight).

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

STIEVA-A Cream also includes the following excipients: butylated hydroxytoluene, butylated hydroxyanisole, disodium edetate, isopropyl palmitate, methyl hydroxybenzoate, propyl hydroxybenzoate, PEG-40 stearate, propylene glycol, stearic acid, stearyl alcohol, soft, white paraffin, purified water, titanium dioxide\*.

\*Please note titanium dioxide is present in STIEVA-A 0.1% cream formulation only.

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 SHELF LIFE**

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

For STIEVA-A Cream 0.025% and 0.05%:

Store below 30°C.

Do not freeze.

For STIEVA-A Cream 0.1%:

Store below 25°C.

## 6.5 NATURE AND CONTENTS OF CONTAINER

STIEVA-A Creams 0.025%, 0.05% and 0.1% are supplied in epoxy-lined aluminium tubes in pack sizes of 3 g (physician's sample for 0.025% and 0.1% only), 6 g (0.1% only) and 25 g.

Not all strengths or pack sizes may be distributed in Australia.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

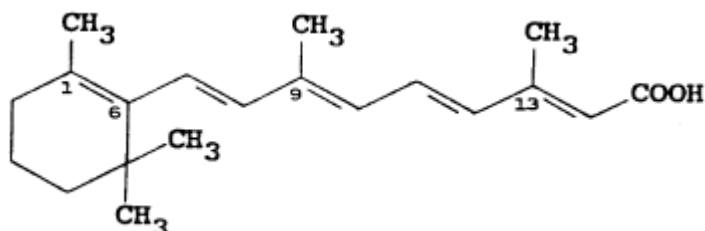
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Chemical names: 3, 7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexene-1-yl)-2,4,6,8-non-tetraenoic acid; all-trans-retinoic acid; tretinoin.

Molecular formula: C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>. Molecular weight: 300.4.

### Chemical structure



### CAS number

302-79-4

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067



## 9 DATE OF FIRST APPROVAL

15 May 1992

## 10 DATE OF REVISION

19 October 2018

### SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI Re-format
4.3, 4.4, 4.6	Included pregnancy as a contraindication

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