

# Stieva-A

Tretinoin Preparations

## Name of medical preparation

Stieva-A cream

## Formulations and Strength

Topical cream containing tretinoin 0.01 % w/w (0.01 g per 100 g cream)

Topical cream containing tretinoin 0.025 % w/w (0.025 g per 100 g cream)

Topical cream containing tretinoin 0.05 % w/w (0.05 g per 100 g cream)

Topical cream containing tretinoin 0.1 % w/w (0.1 g per 100 g cream)

Not all presentations may be marketed locally.

## Excipients

Butylated hydroxytoluene

Butylated hydroxyanisole

Edetate disodium

Isopropyl palmitate

Methylparaben

Polyoxyl stearate

Propylparaben

Propylene glycol

Purified Water

Stearic acid

Stearyl alcohol

Titanium dioxide\*

Petrolatum white

\* Only in Stieva-A Forte Cream 0.1% w/w

For important information about some of these excipients see Warnings and Precautions.

## CLINICAL INFORMATION

### 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.

Stieva-A Cream should be used for dry and sensitive skin.

### Pharmaceutical form:

Topical cream

### **Route of Administration**

For topical application only.

### **Recommended dosage**

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.

Therapeutic effects may not be seen until 8-10 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 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.

- **Children**

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.

- **Elderly**

There are no specific recommendations for use in the elderly.

- **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 Pharmacokinetics*).

- **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 Pharmacokinetics*).

### **Contraindications**

- Patients with known hypersensitivity to any of the ingredients should not use Stieva-A.
- Stieva-A should not be used in patients with a personal or family history of cutaneous epithelioma.
- Pregnancy
- Women planning a pregnancy

### **Warnings and Precautions**

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.

Due to potential for severe irritation, application to eczematous skin should be avoided.

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 occurs, 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.

STIEVA-A cream contains paraffin. Instruct patients not to smoke or go near naked flames due to the risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

## **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).

## **Pregnancy and Lactation**

### **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 (*see Non-clinical Information*).

### **Pregnancy**

Stieva-A is contraindicated in pregnancy, or in women planning a pregnancy. If the 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, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) 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.

### **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.

### **Ability to perform tasks that require judgement, motor or cognitive skills**

With only negligible percutaneous absorption of tretinoin from topical preparations, no detrimental effects on such activities are predicted from the adverse reaction profile of topical tretinoin.

### **Adverse Reactions**

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

Very common:	$\geq 1/10$
Common:	$\geq 1/100$ to $< 1/10$
Uncommon:	$\geq 1/1000$ to $< 1/100$
Rare:	$\geq 1/10000$ 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.

#### ***Topical Cream***

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.

## **Overdosage**

### **Symptoms and signs**

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 25 g tube would contain 25 mg tretinoin. Oral ingestion of a 25 g tube of Stieva-A cream 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 or as recommended by the National Poisons Centre, where available.

## **Clinical Pharmacology**

### **Pharmacodynamics**

#### **ATC code**

Pharmacotherapeutic group: retinoids for topical use in acne, tretinoin.

ATC code: D10AD01

### **Mechanism of action in acne**

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.

### **Pharmacodynamic effects**

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.

### **Pharmacokinetics**

#### **Absorption**

The percutaneous absorption of 0.1% w/w <sup>14</sup>C-labelled retinoic acid was studied in six adult male volunteers. No systemic toxic effects have been reported following topical administration of different formulations of tretinoin.

In patients pre-treated with unlabelled tretinoin, slight increases in blood radioactivity were observed 8 hours after application of the radiolabelled material. In patients not pre-treated, no significant increases in radioactivity were observed.

#### **Distribution**

Tretinoin was minimally detectable in the horny layer and sebaceous glands of normal skin two and four hours after application of radio-labelled tretinoin. Appreciably higher levels were found in the hair follicles and apocrine glands. Twenty-four hours after application, no penetration of radioactivity was detected lower than the Malpighian layer.

#### **Metabolism**

Tretinoin appears to form inactive oxidation products which are excreted in the urine, and glucuronides which are excreted in the faeces.

Limited data are available in humans.

#### **Elimination**

Urine recovery studies in subjects not pre-treated with tretinoin 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 pre-treated subjects. Extraction of radioactivity from skin occlusive dressings accounted for 73% to 96% (mean: 85.9%) of the applied dose.

### **Special patient populations**

- **Children**

Not relevant for this product.

- **Elderly**

No additional information.

- **Renal impairment**

*See Dosage and Administration*

- **Hepatic impairment**

*See Dosage and Administration*

## **NON-CLINICAL INFORMATION**

### **Carcinogenesis/Mutagenesis**

Carcinogenicity testing has not been performed with tretinoin in any species.

Studies in hairless mice suggest that concurrent dermal exposure to isotretinoin at a dose of 100 mg/kg may enhance the tumorigenic potential of UV irradiation. The relevance of this finding to humans is unknown.

Tretinoin was negative in the Ames assay at 2000 µg/plate with and without S9 metabolic activation.

### **Reproductive Toxicology**

#### **Fertility**

The effects of orally administered tretinoin on fertility and early embryonic development were studied in mice and rats. Pre-implantation embryonic development was not affected at doses up to 100 mg/kg in mice. General reproductive performance was not affected at doses up to 2 mg/kg/day in rats.

#### **Pregnancy**

Topical application of high doses of tretinoin induces maternal toxicity, which limits the maximum dose to a level potentially below that associated with embryofetal alterations by other routes of administration.

However, teratogenicity as a result of topical application of tretinoin has been demonstrated in animals.



**Presentation**

Stieva-A Cream is supplied in epoxy-lined aluminium tubes of 25 g capacity. The tube is presented in a carton with a package leaflet.

**Storage**

The storage conditions are detailed on the packaging.

Do not freeze.

**Incompatibilities**

No incompatibilities have been identified.

**Product owner:**

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