AUSTRALIAN PRODUCT INFORMATION – RETRIEVE® (TRETINOIN) CREAM

1 NAME OF THE MEDICINE

Tretinoin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ReTrieve Cream contains tretinoin 0.05% w/w (0.5mg/g).

Excipients with known effect: Contains hydroxybenzoates and diazolidinyl urea.

3 PHARMACEUTICAL FORM

Cream, topical.

ReTrieve is a soft, smooth off-white to pale yellow homogenous glossy cream.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ReTrieve Cream is indicated for:

- Adjunctive treatment of dry photoaged skin and related conditions
- Treatment of acne vulgaris, in particular forms where comedones, papules and pustules predominate in patients 12 years of age and older. It is not generally effective in most cases of severe pustular or nodulocystic acne.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with tretinoin should be individualised according to tolerance and response. No other topical preparations should be applied over the nightly inunction, but suitable moisturisers may be used during the day.

Certain types of skin could be too sensitive to use ReTrieve Cream. Patients with very sensitive skin should consult a dermatologist before commencing treatment.

Dose

Dry Photoaged Skin:

ReTrieve should be applied sparingly to the affected areas once daily at bedtime.

Acne Vulgaris:

ReTrieve should be applied sparingly to the affected areas once daily at bedtime. Therapeutic effects may not be seen until several weeks after the start of treatment. Treatment should normally be continued for three months. Treatment should not exceed three months of continuous use without careful evaluation.

Method of administration

Begin the treatment program slowly, as follows:

1. Wash the affected areas prior to any application with mild soap free cleansers and pat dry.

2. First night: apply, leave for five minutes, then wash off.

3. Second night: apply, leave for ten minutes, then wash off.

4. Third, fourth, fifth and sixth nights: increase the treatment time each night by 30 minutes until the application is left on for two hours.

5. If, after a two hour application, no redness or irritation has developed on the skin the following day, then the application may be left on overnight and washed off next morning.

6. If excessive skin reactions occur, adjust the schedule to alternate nights until the skin accommodates.

4.3 CONTRAINDICATIONS

- Pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION)
- Women planning a pregnancy
- Hypersensitivity to tretinoin or any of the ingredients in the formulation

Retrieve should only be given to women of childbearing potential that are using effective contraception correctly during treatment and for 1 month after discontinuation of treatment.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Concomitant Use with Other Topical Preparations:

Concomitant application of other topical preparations including cosmetics should be avoided because of possible incompatibility and interaction with tretinoin.

Particular caution should be exercised in the use of keratolytic agents such as sulphur, salicylic acid, benzoyl peroxide or resorcinol and chemical abrasives. If the patient has been treated with such preparations, the effect of the peeling agents must subside before any commencement of topical ReTrieve therapy.

Some medicated cleansers and scrubbing solutions have a strong drying effect. They should not be used in patients receiving tretinoin topical therapy.

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.

Skin and Mucous Membrane Irritation:

Particular caution is indicated for patients with eczema, since tretinoin has been reported to cause severe irritation on eczematous skin.

Extreme weather conditions, such as strong wind or cold dry air may cause skin irritation to patients receiving tretinoin treatment.

Do not swallow and avoid contact with mucous membranes or open wounds.

ReTrieve should not be applied to the eyes, mouth, lips, mucosa, or angles of the nose.

Should any of these occur, rinse the affected areas thoroughly with water to avoid local irritation.

The hands should be washed thoroughly with water after each application.

Over enthusiastic use or too frequent application may cause redness, stinging and discomfort. If severe irritation occurs, especially in the early stage of therapy, patient should be advised to discontinue temporarily or reduce the frequency of application.

Use in patients with a history of acute eczemas, rosacea and perioral dermatitis:

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.

Use in patients with a personal or familial history of skin cancer:

Patients receiving tretinoin are more susceptible to the effect of UV irradiation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Ultraviolet Exposure). A 91-week dermal study in mice using topical tretinoin was associated with the development of squamous cell carcinomas and papillomas in female mice at the site of application (see Section 5.3 PRECLINICAL SAFETY DATA). The risks and benefits of use of ReTrieve in patients with a personal or family history of skin cancer should be carefully considered.

Ultraviolet Exposure:

Exposure of the treated areas to sunlight including sunlamps should be minimised during the course of topical treatment with ReTrieve.

Patients receiving tretinoin treatment are more susceptible to the effect of UV irradiation especially at the start of the therapy. Animal studies suggest that tretinoin may accelerate the tumorigenic potential of ultraviolet radiation in hairless albino mice, especially at high concentrations of the drug. Although the significance to human is unknown, patients undergoing tretinoin treatment should exercise utmost caution.

Patients with sunburn should be advised to use ReTrieve only after the skin is fully recovered.

Exposure to ultraviolet irradiation increases the intensity of inflammatory reaction. Patients receiving ReTrieve therapy should avoid exposure to artificial sunlamps or solarium.

Patients should be counselled to routinely use high SPF sunscreens as well as protective clothing while undergoing ReTrieve topical treatment, especially those individuals at risk of chronic sun exposure or having a family history of light sensitivity.

Use in hepatic impairment

No data available

Use in renal impairment

No data available

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant use of other topical medications (especially those containing keratolytic agents such as resorcinol, sulphur, salicylic acid, benzoyl peroxide and abrasive chemicals etc.) should be avoided in patients undergoing treatment with ReTrieve because of possible interactions with tretinoin. The application of ReTrieve should only commence after the effect of the peeling agents has completely subsided (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Tretinoin is an unstable compound that is often incompatible with substances found in topical preparations.

Some topical products and certain cosmetics contain high concentrations of alcohol, spices, lime, or menthol. They should be used with caution especially in the early phase of treatment due to stinging action of these chemicals.

ReTrieve Cream should not be administered if the patient is also taking medicines known to be photosensitisers (e.g., thiazides, tetracyclines, flluoroquinolones, phenothiazines, sulphonamides) because of the possibility of augmented phototoxicity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy – Pregnancy Category D

There have been isolated reports of birth defects in babies born to women using topical tretinoin in pregnancy. To date, there have been no adequate and well controlled prospective studies in women using topical tretinoin in pregnancy. A retrospective cohort study of babies born to 215 women exposed to topical tretinoin during the first trimester of pregnancy found no more birth defects among these babies than those born to 430 women in the same cohort who were not similarly exposed.

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 in 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.

Oral tretinoin has been shown to be teratogenic in rats when given at doses of 5 mg/kg/day and fetotoxic in rats when given at doses of 2.5 mg/kg/day. Oral doses of tretinoin have caused limb defects in mice.

However, 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.

These latter changes may be considered variants of normal development and are usually corrected after weaning.

ReTrieve is contraindicated in pregnancy, or in women planning a pregnancy (see Section 4.3 CONTRAINDICATIONS). If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Women of childbearing potential

ReTrieve should only be given to women of childbearing potential that are using effective contraception correctly during treatment and for 1 month after discontinuation of treatment. ReTrieve is contraindicated in women of childbearing potential not using an effective method of contraception properly.

Use in lactation

Safe use during lactation has not been established. It is not known whether this drug is excreted in human milk. Therefore, use during lactation is not recommended.

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)

ReTrieve is generally well tolerated after nightly application. Some patients may experience a transitory sensation of warmth or slight stinging after application of the drug.

If excessive reactions occur, the frequency of application may be reduced or treatment discontinued temporarily until the reactions subside. The dose and frequency may then be adjusted to a level which the patient can tolerate (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Increased sensitivity to UV light may be experienced in patients undergoing treatment and appropriate measures should be taken (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dry Photoaged Skin:

Side effects have been limited to mild irritation, evidenced by peeling and erythema, especially in the early stage of treatment.

Temporary hyperpigmentation or hypopigmentation has occurred with repeated topical application of the drug.

Contact allergy has been reported in isolated instances.

Reversible changes in liver function tests have been reported after administration of tretinoin topical therapy but do not appear to be of clinical significance. Elevated serum level of bilirubin, alkaline phosphatase, glutamic-pyruvic transaminase, glutamic oxaloacetic transaminase and increase in thymol turbidity and flocculation were observed but in all cases reported, the results reverted to normal on discontinuing treatment.

Acne Vulgaris:

The following safety information is sourced from an Australian tretinoin cream Product Information:

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

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

Post-marketing data for other topical tretinoin creams has reported pyogenic granuloma-like lesions as a rare adverse event.

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.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

No data are available on the consequences of overdosage from accidental ingestion of ReTrieve. Tretinoin is a normal metabolite of vitamin A and has similar toxicity profile. The LD_{50} of tretinoin in mice and rats has been found to be 4g/kg and 2g/kg respectively.

The concentration of tretinoin present in ReTrieve at 0.5mg/g is unlikely to cause any symptomatic effects. Any acute toxicity arising from accidental ingestion of the preparation will be more related to the toxicity of the vehicle components. Accidental ingestion should be managed clinically.

Symptoms of acute toxicity would be of gastrointestinal disturbance.

Overdosage from excessive dermal application may produce marked erythema and skin inflammatory reactions. Should this occur, discontinue use and if necessary, apply cold compresses and/or mild emollient.

5 PHARMACOLOGICAL PROPERTIES

Tretinoin, being a metabolite of retinol, is both pharmacologically and structurally related to vitamin A which regulates cell growth and differentiation. It has been postulated that it acts by enhancing epithelial proliferation and accelerating epithelial differentiation.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tretinoin, an all-*trans* retinoic acid, occurs in the body as a tissue metabolite of vitamin A. The precise mechanism of action of topical tretinoin has not been fully elucidated.

For treatment of acne topical tretinoin has comedolytic, anti-comedogenic and anti-inflammatory effects. Tretinoin decreases cohesiveness of follicular epithelial cells resulting in decreased microcomedone formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells, causing extrusion of the comedones. The comedolytic activity is related to a normalisation of the desquamation of the follicular epithelium. Tretinoin exerts anti-inflammatory effects via suppression of toll-like receptors (TLRs).

Clinical trials

<u>Photoaged Skin Indication</u>:

No data available

<u>Acne Vulgaris Indication:</u>

The results of a number of published studies support the efficacy of tretinoin 0.05% cream in the treatment of acne vulgaris.

Published studies include, Trifu *et al*[1], Fatum *et al*[2], Cunliffe[3].

Trifu *et al* conducted a pilot randomised, double-blind study evaluated the efficacy and safety of cortexolone 17α-propionate (CB-03-01) 1% cream in men with mild-to-moderate facial acne vulgaris, compared with placebo and tretinoin 0.05% cream. Seventy-seven participants were treated once daily for 8 weeks (CB-03-01 n=30; tretinoin n=32; placebo n=15). The primary objective was to compare CB-03-01 with placebo for changes in total lesion count (TLC), inflammatory lesion count (ILC), acne severity index (ASI), and Investigator's Global Assessment (IGA), with secondary comparison versus tretinoin. At week 8, mean percentage reductions were 65.7% (CB-03-01), 52.5% (tretinoin), and 37.0% (placebo) for TLC; 67.3%, 50.7%, and 39.0% for ILC; and 68.4%, 53.1%, and 39.5% for ASI, respectively.

Key limitations of the study included the pilot design, small sample size, and unequal treatment groups, particularly the small placebo arm. The study enrolled only adult men and had a short treatment duration (8 weeks), restricting generalisability and assessment of longer-term outcomes.

Fatum *et al* conducted a randomised, double-blind multicentre study which investigated the efficacy and tolerability of topical 0.1% motretinide cream, 0.05% tretinoin cream, and placebo cream in 167 patients with acne vulgaris treated in general practice. After 6–8 weeks, all groups showed a reduction in acne lesions, but tretinoin demonstrated a greater median decrease in total lesion count (11.3) compared to motretinide (8.1) and placebo (6.4). Tretinoin was statistically superior to both motretinide and placebo for reducing pustules and overall lesion count, while all treatments were similarly effective against comedones. Papules responded better to tretinoin than placebo.

Limitations of the study include a smaller sample size than planned, a notable dropout rate, and non-randomised dose reduction in the tretinoin group due to irritation. Local side effects such as erythema, peeling, and burning were significantly more frequent and severe with tretinoin, while motretinide and placebo had similar tolerability profiles.

A multicentre, randomised, investigator-blinded trial by Cunliffe *et al* compared the efficacy and tolerability of tretinoin cream 0.05% and adapalene gel 0.1% in 409 patients aged 12–25 years with mild-to-moderate acne vulgaris over a 10-week period. Both treatment groups showed similar reductions in inflammatory lesion counts (tretinoin: 21.0 to 14.0; adapalene: median

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[1] Cortexolone 17a-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized, double-blind comparative study vs. placebo and tretinoin 0.05% cream - by V. Trifu *at el*, British Journal of Dermatology, 2011, 165 pp177–183

[2] Topical treatment of acne vulgaris with vitamin A acid derivative motretinide (Tasmaderm®), tretinoin (Airol®) and placebo cream - by Bjarne Fatum, Hans-Henrik V. Hansen, Erik Mortensen, Birgit Ohrt Mikkelsen, and Kirsten Møllenbach, Weekly Journal for Medical Doctors (Ugeskrift for Læger), issued by the Danish Medical Association, Volume 142, Issue 51, 15 December 1980, pages 3361-3442

[3] Randomised, controlled trial of the efficacy and safety of adapalene gel 0.1% and tretinoin cream 0.05% in patients with acne vulgaris by W.J. Cunliffe and colleagues, European Journal of Dermatology, Volume 12, Issue 4, July–August 2002

reduced from 20.5 to 13.0), non-inflammatory lesion counts (both groups reduced from approximately 49–50 to 25), and total lesion counts (both groups reduced from 73.0 to 39.0). The proportion of patients showing marked or moderate improvement, or almost total clearance, was also similar between tretinoin (57.7%) and adapalene (59.6%).

Local side effects such as erythema, dryness, desquamation, and stinging or burning sensations were reported. No serious adverse events were reported in either group. Limitations include the absence of a placebo comparator, as both groups received active treatments, and the study population was predominantly Caucasian with mild-to-moderate acne. Results were not stratified by age, sex, or acne severity, and systemic laboratory safety parameters were not assessed.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Topically applied tretinoin appears to be slightly absorbed from the skin.

Metabolism & Excretion

Unlike retinol and its esters, it does not accumulate in the body but metabolises rapidly and excretes in the form of inactive glucuronides or oxidation products. These metabolites are mainly excreted in the faeces and some oxidised metabolites are found in the urine.

In vitro studies in human skin showed that only a small percentage of the applied dose could be detected in urine.

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 aneuplodogenic 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Ultraviolet Exposure).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ReTrieve cream contains the following inactive ingredients: Cetyl alcohol, diazolidinyl urea, disodium edetate, dl-alpha tocopheryl acetate, glyceryl monostearate, isopropyl palmitate, methyl hydroxybenzoate, polysorbate 60, propylene glycol, propyl hydroxybenzoate, retinol palmitate, sorbitan monostearate and purified water.

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

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Contained in a metal (aluminium) tube with an outer carton and is available in the following pack sizes:

-5g tube

-10g tube*

-50g tube

* - not currently distributed in Australia

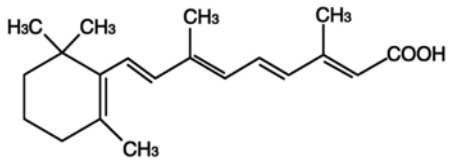
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Tretinoin is a yellow to light orange crystalline powder. It is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol (96 per cent).

Chemical structure



CAS number

302-79-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Ltd

Level 10, 12 Help St,

Chatswood, NSW 2067

Toll-free Number: 1800 630 056

9 DATE OF FIRST APPROVAL

20 September 1991

10 DATE OF REVISION

20 January 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Sections 4.1, 4.9	Inclusion of acne vulgaris indication and associated safety information.
Section 5.1	Removal of reference to gastric lavage.