AUSTRALIAN PRODUCT INFORMATION – RETRIEVE® (TRETINOIN) CREAM

1 NAME OF THE MEDICINE

Tretinoin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

ReTrieve Cream contains tretinoin 0.05% w/w (0.5mg/g) in a smooth, off-white to pale yellow hydrophilic cream base of 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.

Excipient with known effect:

Hydroxybenzoates, diazolidinyl urea.

3 PHARMACEUTICAL FORM

Cream, topical.

Tretinoin (ReTrieve) 0.05% w/w cream – Smooth off-white to pale yellow.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adjunctive treatment of dry photoaged skin and related conditions.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

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.

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

4.3 CONTRAINDICATIONS

- Pregnancy
- Women planning a pregnancy
- Hypersensitivity to tretinoin or any of the ingredients in the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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.

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. Particular caution is indicated for patients with eczema, since tretinoin has been reported to cause severe irritation on eczematous skin. 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 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. If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

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. Side effects have been limited to mild irritation, evidenced by peeling and erythema, especially in the early stage of treatment. 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 till the reactions subside. The dose and frequency may then be adjusted to a level which the patient can tolerate.

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

Contact allergy has been reported in isolated instances.

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).

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.

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.

Symptoms of acute toxicity would be of gastrointestinal disturbance. In such event, treatment such as gastric lavage, inducing emesis and/or forced fluids should be performed as soon as possible.

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.

Clinical trials

No data available

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

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

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

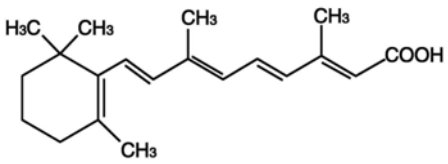
* - not currently distributed in Australia

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

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

9 DATE OF FIRST APPROVAL

20 September 1991

10 DATE OF REVISION

05 September 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted to new version
All	Updated to new format (March 2018)
Sections 4.3 & 4.6	Safety-related request (SSR) - updated the Contraindications section and Precautions section as requested by SIU, PSAB, TGA.