Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Retin-A 0.05% w/w Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tretinoin 0.05 % w/w.

Excipients: Also contains Butylhydroxytoluene (E321) 0.1% w/w, Sorbic Acid 0.2% w/w and Stearyl Alcohol 3.0% w/w

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream.
Smooth pale yellow cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the management of acne vulgaris and other keratotic conditions.

4.2 Posology and method of administration

For cutaneous administration.

4.2.1 Adults

Acne:

Retin-A should be applied once or twice daily to the area of the skin where acne lesions occur.

Before application of Retin-A, areas to be treated should be cleansed thoroughly with water and a mild, non-medicated soap. The treated area should be washed no more than twice a day. After washing, the skin should be dried gently and completely without rubbing it. Areas of the skin being treated should be allowed to dry for at least 20 to 30 minutes before application of Retin A.

Only apply sufficient to cover the affected areas lightly, using a gauze swab, cotton wool or the tips of clean fingers. Avoid over-saturation to the extent that excess medication could get into the eyes, angles of the nose or other areas where treatment is not intended.

Initial applications may cause transitory stinging and a feeling of warmth. The correct frequency of administration should produce a slight erythema similar to that of mild sunburn.

If Retin-A is applied excessively, no more rapid or better results will be obtained and marked redness, peeling or discomfort may occur, should this occur accidentally or through over enthusiastic use, application should be discontinued for a few days.

Patience is needed in this treatment, since the therapeutic effects will not usually be observed until after 6-8 weeks of treatment. During the early weeks of treatment, an apparent exacerbation of inflammatory lesions may occur. This is due to the action of the medication on deep, previously unseen comedones and papules.

Once the acne lesions have responded satisfactorily, it should be possible to maintain the improvement with less frequent applications.

Moisturisers and cosmetics may be used during treatment with Retin-A, but should not be applied to the skin at the same time. The skin should be thoroughly washed before application of Retin-A. Astringent toiletries should be avoided.

4.2.2 Children

Safety and effectiveness have not been established in children.

4.3 Contraindications

- History of sensitivity/hypersensitivity reactions to any of the components
- Pregnancy
- Evidence of skin damage
- Personal or familial history of cutaneous epitheliomata or eczema

4.4 Special warnings and precautions for use

1. The frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance.

2. The presence of cutaneous irritative signs (e.g. erythema, peeling, pruritus, sunburn, etc) should prohibit initiation or recommencement of treatment with Retin-A until the symptoms resolve.

3. Following prolonged use of peeling agents it is advisable to 'rest' a patient's skin until the effects of the peeling agent subside before the use of Retin-A is begun. When Retin-A and peeling agents are alternated, contact dermatitis may result and frequency of application may have to be reduced.

4. Avoid contact with eyes, eyelids, nostrils, mouth and mucous membranes. If contact in these areas occurs, careful washing with water is recommended.

5. In certain sensitive individuals, topical use may induce severe local erythema, swelling, pruritus, warmth, burning or stinging, blistering, crusting and/or peeling at the site of application. If the degree of local irritation warrants, the patient should be directed to apply the medication less frequently or discontinue its use temporarily. If a patient experiences severe or persistent irritation, the patient should be advised to discontinue application of Retin-A completely and if necessary, consult a physician.

   Weather extremes, such as wind or cold and low humidity, may also be irritating to skin being treated with Retin-A and may increase its dryness.

   Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

   Patients will be able to remove hair as usual (e.g. plucking, electrolysis, depilatories) but should avoid these procedures before applying Retin-A as they might result in skin irritation.

   Permanent wave solutions, waxing preparations, medicated soaps and shampoos can sometimes irritate even normal skin. Caution should be used so that these products do not come into contact with skin treated with Retin-A.

   Exposure to sunlight
   Exposure to sunlight, including ultraviolet sunlamps, should be avoided or minimised during the use of tretinoin. Patients with sunburn should be advised not to use the product until fully recovered because of potential severe irritation to skin.

A patient who experiences considerable sun exposure due to occupational duties and/or anyone inherently sensitive to the sun should exercise particular caution. When exposure to sunlight cannot be avoided, use of sunscreen products and protective clothing over treated areas is recommended.

6. **Warning**: the weight of evidence indicates that topical tretinoin is not carcinogenic. In a lifetime study of cd-1 mice, a low incidence of skin tumours was seen at 100 and 200 times the estimated clinical dose but, although no such tumours were seen in the study controls, the incidence in these treated animals was within the historic control range for cd-1 mice. Studies in hairless albino mice suggested that tretinoin may accelerate the tumorigenic potential of UVB light from a solar simulator.

   In other studies, when light pigmented hairless mice treated with tretinoin were exposed to carcinogenic doses of UVB light, the photocarcinogenic effects of tretinoin were not observed. Due to significantly different experimental conditions, no strict comparison of this disparate data is possible. Although the significance of these studies in man is not clear, patients should avoid or minimise exposure to sunlight.

   The weight of evidence indicated that topical tretinoin is not mutagenic. The mutagenic potential of tretinoin was evaluated in the Ames assay and *in-vivo* mouse micronucleus assay, both of which showed negative findings.

7. History of sensitivity/hypersensitivity to any of the components as part of the combined statement in Contraindications.

4.5 Interaction with other medicinal products and other forms of interaction

The following products or medications should be used with caution because of possible interaction with tretinoin. It is advised to allow the effects of such preparations to subside before use of Retin-A is begun:

- concomitant topical medication
- preparations containing benzoyl peroxide
- toiletry preparations having an abrasive, drying, or desquamative effect, including soaps, shampoos, cosmetics, and products with high concentrations of alcohol, astringents, spices or lime.

4.6 Fertility, pregnancy and lactation

In animal reproductive studies, oral tretinoin is known to be teratogenic and has been shown to be foetotoxic in rats when given in doses 500 times the topical human dose. In reproduction studies in rats and rabbits, topical tretinoin, when used at doses of 500 and 320 times the topical human dose, respectively, induced minor skeletal abnormalities e.g. irregularly contoured or partially ossified skull bones.

These changes may be considered variants of normal development and are usually corrected after weaning. Retin-A should not be used during pregnancy. It is not known whether tretinoin is excreted in human milk, therefore caution should be exercised when Retin-A is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Retin-A is administered topically and is unlikely to have an effect on one’s ability to drive or operate machinery.

4.8 Undesirable effects

The safety of tretinoin topical formulations including Retin-A was evaluated in 4160 patients (of whom 3035 were treated with topical tretinoin and 1125 received placebo) who participated in 23 clinical trials, including 4 open-label and 19 double-blind, placebo-controlled clinical trials. The 23 clinical trials evaluated the safety of tretinoin in male and female patients, aged 10 to 79 years, with photodamaged skin or acne vulgaris.

The table below displays ADRs that have been reported with the use of tretinoin topical formulations from the 23 clinical trials and from postmarketing experience.

The displayed frequency categories use the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

Table: Adverse Drug Reactions Reported in Clinical Trials and Postmarketing Experience for RETIN-A

System Organ Class	Adverse Drug Reactions			
	Frequency Category			
	Very Common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Immune System Disorders				Hypersensitivity
Nervous System Disorders		Headache		
Eye Disorders			Eye irritation	
Skin and Subcutaneous Tissue Disorders	Hyperkeratosis, Pain of skin	Skin irritation, Erythema, Pruritus, Rash papular, Rash, Dermatitis, Dry skin, Skin exfoliation	Swelling face, Blister, Skin discolouration, Skin burning sensation, Photosensitivity reaction, Urticaria	Skin hyperpigmentation, Skin hypopigmentation, Scab
General Disorders and Administration Site Conditions			Feeling hot	

4.9 Overdose

Excessive application of Retin-A does not improve the results of treatment and may induce marked irritation, e.g. erythema, peeling, pruritus, etc. Oral ingestion of Retin-A may lead to the same effects associated with excessive oral intake of vitamin A (e.g. pruritus, dry skin, arthralgias, anorexia, vomiting). In the event of accidental ingestion, if the ingestion is recent, an appropriate method of gastric emptying should be used as soon as possible.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Retinoids for topical use in acne
ATC code: D10AD01

Tretinoin (ß-All trans retinoic acid, vitamin A acid) produces profound metabolic changes in keratinizing epithelia. Tretinoin increases the proliferative activity of epidermal cells in *in vivo* and *in vitro* studies, and cellular differentiation (keratinization and cornification) is also altered.

5.2 Pharmacokinetic properties

Absorption
Tretinoin is an endogenous metabolite of Vitamin A metabolism in man. Upon topical application, tretinoin is minimally absorbed, penetrating both the epidermis and dermis.

Percutaneous absorption of tretinoin, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in healthy men and women after single and/or repeated daily applications of a 0.05%, 0.1% or 0.5% tretinoin cream formulation or a 0.01% tretinoin gel formulation, at doses of 100, 150 or 500 mg. The mean percutaneous absorption ranged from 1.0 to 4.3%.

Endogenous plasma concentrations of tretinoin and its metabolites, 13-cis-retinoic acid, all-trans-4-oxo-retinoic acid and 13-cis-4-oxo-retinoic acid were essentially unaltered after either single or multiple daily applications relative to baseline levels.

Distribution
Approximately 80% of tretinoin applied remains on the skin surface, whereas its penetration through the stratum corneum and the hair follicle is vehicle-dependent. After the initial diffusion into the stratum corneum that occurs within a few minutes, further diffusion into epidermis and dermis proceeds more slowly.

Metabolism
Topically-applied tretinoin is metabolized by CYP2S1 and CYP26. Metabolites are 13-cis-retinoic acid, all-trans-4-oxo-retinoic acid and 13-cis-4-oxo-retinoic acid.

Elimination
After application of radiolabelled tretinoin emollient cream or cream, urinary excretion occurred mainly in the first 48 hours, whereas radioactivity was eliminated in the faeces throughout the 7 days after dose application. On average 1 – 1.5% of the radioactivity was recovered in urine and less than 1 % was recovered in feces.

Paediatric Population
It is expected that pharmacokinetic behavior of tretinoin topical formulations and drug-drug interactions with tretinoin topical formulations will be similar to those in adults. In a study in 20 adolescent patients with moderate to severe acne treated for 12 weeks with tretinoin gel, none of the plasma samples obtained at Week 12 of the treatment period contained quantifiable tretinoin levels.

5.3 Preclinical safety data

Topical administration of Retin-A products produces dose-dependent erythema, peeling and irritation and excessive use of the products should be avoided. Retin-A 0.1% w/w did not produce an allergic response when tested in 160 subjects by the Draize test.

No systemic toxic effects have been reported following topical application of Retin-A formulations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene (E321)
Isopropyl myristate
Macrogol stearate 40 Sorbic acid (E200)
Stearic Acid 50 (E570)
Stearyl alcohol
Xanthan gum (E415)
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium tube lined with epoxy resin or epoxy resin with wax, with tube screw cap of polyethylene or urea resin, containing 20 g or 60 g of cream.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 748/33/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th January 1978
Date of last renewal: 12th January 2008

10 DATE OF REVISION OF THE TEXT

January 2013