1. Name of the Medicinal Product

Tretinoin Cream 0.025 % w/w

2. Qualitative and Quantitative Composition

Tretinoin BP 0.025 % w/w Cream

Base q. s.

3. Pharmaceutical Form

Topical 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

Adults: Tretinoin cream 0.025% w/w Cream should be applied once or twice daily to the area of skin where acnelesions occur. 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 run into the eyes, angles of the nose or other areas where treatment is not intended. Initial application 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 Tretinoin cream 0.025% w/w Cream 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 oftreatment. 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 come dones 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 Tretinoin cream 0.025% w/w Cream but should not be applied to the skin at the same time. The skin should be thoroughly washed before application of Tretinoin cream. Astringent toiletries should be avoided.

Children

The safety and efficacy of tretinoin in children aged less than 10 years has not been established.

4.3 Contraindications

Tretinoin cream 0.025% w/w cream is contraindicated in patients with: - A history of sensitivity/hypersensitivity reactions to any of the components - Pregnancy - Personal or familial history of cutaneous epithelioma - Acute eczemas (as tretinoin has been reported to cause severe irritation on eczematous skin) - Rosacea and perioral dermatitis

4.4 Special Warnings and Precautions for use

The skin of certain sensitive individuals may become excessively red, edematous, blistered, or crusted. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the medication should be adjusted to a level the patient can tolerate. True contact allergy to topical tretinoin is rarely encountered. Temporary hyper-or hypopigmentation has been reported with repeated application of Tretinoin cream. Some individuals have, been reported to have heightened susceptibility to sunlight while under, treatment with Tretinoin cream. To date, all adverse effects of Tretinoin cream have been reversible upon discontinuance of therapy.

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 it. It is advised to allow the effects of such preparations to subside before use of cream 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 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 500 and 320 times the topical human dose, respectively, induced minor skeletal abnormalities, eg irregularly contoured or partially ossified skull bones. These changes may be considered variants of normal development and are usually corrected after weaning. Tretinoin cream 0.025% w/w Cream should not be used during pregnancy. It is not known whether tretinoin is excreted in human milk, therefore caution should be exercised when Tretinoin cream 0.025% w/w Cream is administered to a nursing mother

4.7 Effects on ability to drive and use machines Not Applicable.

4.8 Undesirable effects

Skin and subcutaneous disorders

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Skin and subcutaneous tissue disorders Very common:

Application site erythema, skin exfoliation, skin pain, application site pruritus, skin irritation, skin tenderness, skin burning sensation, application site stinging, dry skin Post-marketing data:

The following adverse drug reactions are based on post-marketing reports. Since these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency, however in reality the following reactions are rarely seen. Skin and subcutaneous tissue disorders Not known:

Skin hyperpigmentation, skin hypopigmentation, photosensitivity reaction

4.9 Overdose

Excessive application of Tretinoin cream 0.025% w/w Cream does not improve the results of treatment and may induce marked irritation, eg erythema, peeling, pruritus, etc. Oral ingestion of Tretinoin cream 0.025% w/w Cream may lead to the same effects associated with excessive oral intake of vitamin A (eg 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 (ßAll 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

Tretinoin is a known metabolite of vitamin A. It appears to form oxidation products which are excreted in the urine and glucuronides excreted in the feces.

In human cutaneous absorption of retinoic acid was studied by application of 3 grams of 14C labelled 0.1% retinoic acid cream on 200 cm2 of skin. After administration, radio-activity was detected in samples of blood, urine, stool and on skin occlusive dressings.

In subjects pre-treated with unlabelled material, slight increases in their blood radio-activity were observed 8 hours after application of the labelled material. In patients not pre-treated, no significant increases in radio-activity were observed.

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

In a further study, 2 and 4 hours after application of radio-actively labelled tretinoin to normal human skin, tretinoin was minimally detectable in the horny layer and sebaceous glands, but appreciably higher levels were found in the hair follicles and apocrine glands. After 24 hours, no penetration of radio-activity was detected beyond the Malpighian layer. No systemic exposure of clinical significance is expected to arise if renal and hepatic impairment is present during topical use of tretinoin. This is because there is negligible percutaneous absorption of tretinoin when applied topically.

Clinical evaluation of the photosensitivity potential of topical STIEVA-A® cream (0.3%, 0.1% and 0.05%) in one short-term study has shown the preparation to be free of phototoxic properties.

Relatively large systemic doses of tretinoin produced minor changes in the circulatory system of the cat. With 100 mg/kg, reduced perfusion in the hind extremities was noted, but there was no influence on blood pressure or respiration. Using 250 mg/kg, a mild reduction in blood pressure and a slight increase in pulse rate and circulation in the hind extremities were apparent. At a higher dose (1000 mg/kg) a pronounced increase in blood pressure and irregular respiration were observed; cardiac arrest followed fifteen minutes later.

Tretinoin, when administered orally or intraperitoneally, was shown to have a therapeutic effect on chemically induced skin papillomas and skin carcinomas in mice. The extent of the regression of the papillomas appeared to be dependent on the dose and duration of treatment. Tretinoin was also shown to have not only a prophylactic effect on the induction of papillomas but on the development of carcinomas in mice. It has been observed in mice, that tretinoin applied to experimentally produced dermatologic wounds, stimulated wound healing.

The effect of tretinoin on the survival of skin grafts in mice has been investigated. Tretinoin is thought to increase the susceptibility of skin homographs to the process of immunological rejection.

In several studies, tretinoin was administered orally to rats. It appears that little, if any, free tretinoin could be detected in the bile. Retinoyl ß-glucuronide is apparently the only naturally occurring metabolite in rat bile. The glucuronide undergoes ester interchange or dehydration reactions which result in the formation of all trans- or cis-methyl retinoates and retinoyl ßglucurono-g-lactone, respectively. Retinoyl ß-glucuronide was also identified in the liver and intestine.

5.3 Preclinical safety data

Topical administration of Tretinoin cream products produces dose-dependent erythema, peeling and irritation and excessive use of the products should be avoided. Tretinoin cream 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 Tretinoin cream formulations

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cetostearyl Alcohol	BP
Cetomacrogol 1000	BP
Liquid Light Paraffin	BP
Propylene Glycol	BP
Butylated Hydroxy Anisole	IP
Di- Sodium EDTA	BP
White Petroleum Jelly	BP
Sodium Methyl Paraben	BP
Sodium Propyl Paraben	BP
Tween 80	BP
Butylated Hydroxy Toluene	IP
Purified Water	BP

6.2 Incompatibilities Not applicable.

6.3 Shelf life

3 years from the date of manufacture.

6.4 Special precautions for storage Do

not store above 30°C.

Store in the original packaging to protect from moisture

6.5 Nature and contents of container

30 gm tube each packed in a carton along with the Pack Insert.

6.6 Special precautions for disposal and other Special handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT:

Praipec Pharmaceutical Ltd, No 20b Ikemba Road, 1 Ikenga Ogidi Idemili North, Idemili North, Anambra.

MANUFACTURER:

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