1. Name of the Medicinal Product

LEETIN-A (Tretinoin Cream 0.05 % w/w)

2. Qualitative and Quantitative Composition

Tretinoin BP 0.05 % w/w

Cream Base q. s.

3. Pharmaceutical Form

Topical Cream

4. Clinical Particulars

4.1 Therapeutic Indications

Tretinoin is indicated in the treatment of acne vulgaris primarily where comedones, papules and pustules predominate. It is not effective in most cases of severe postular and deep cystic nodular varieties.

4.2 Posology and method of administration

Tretinoin cream is intended for external use only and should be kept away from areas of broken skin, lips, eyes, nose, mouth and other mucous membranes because of its irritant effect.

Because of increases sensitivity of ultraviolet radiation associated with the use of tretinoin, patient should be instructed to use a broad spectrum sunscreen regularly and to wear protective clothing

Tretinoin should be applied sparingly to the affected area once a day before bedtime for up to 12 weeks

Therapeutic results may be noticed after two or three weeks of therapy; however results may not be optimal until after eight to ten weeks of treatment. Once the acne lesions have reported satisfactorily, it may be possible to maintain the improved state with less frequent applications; however a maintenance dose has not been studied or established

Excessive application will not improve efficacy, but may increase the risk of severe irritation

The efficacy and safety has not been studied beyond 12 weeks in acne vulgaris clinical trials

During the first three weeks of treatment; Tretinoin cream may be applied every second day to allow the patient's skin to adjust to the medication, especially for patient with sensitive skin and/or a fair complexion

Formulation strength should be selected and adjusted according to the patient's tolerance.

In case of an apparent exacerbation of the acne lesions during early weeks of therapy, dosing frequency may be reduced or a lower strength of Tretinoin cream may be used.'

Concomitant medicated and non medicated therapies should be used with caution
In cases of undue skin irritations (redness, peeling or discomfort) a moisturiser may be used as needed, the frequency of application should be reduced (e.g. application every other day) use a lower strength of the product; if applicable, or temporarily interrupt treatment. The normal frequency of application should be resumed once the skin irritation subsides. Treatment should be discontinued if skin irritation persists.
Renal Impairment: No dosage adjustment is necessary
Hepatic Impairment: No dosage adjustment is necessary

The area under treatment should be thoroughly cleansed with a mild soap or cleanser; and dried followed by the application of tretinoin cream with a gentle application. Hands should be washed before and after application. Application may be accompanied by a transitory feeling of warmth and stinging sensation. Patients may also use a moisturiser as needed.

Do not apply Tretinoin Cream to eyelids or the skin at the corners of the eyes and mouth. Avoid the angles of the nose, skin folds area and nasolabial fluid. If treatment in these areas is necessary, apply very sparingly. Caution should be used when applying to the sensitive areas of the skin, such as the neck, abraded or eczematous skin, or in patients with inflammatory skin conditions that coexist with acne.
Patients being treated with Tretinoin Cream may continue to use water based, non comedogenic, hypoallergenic and oil-free cosmetics. Following application of Tretinoin Cream the patient should be instructed to allow the skin to dry before applying cosmetics
If combination therapy is required, consideration should be given to the applying the products at different times of the day (eg. one in the morning and the other in the evening)
Missed Dose
If patients forget to take a dose of Tretinoin Cream they should be instructed to apply the next dose at the usual time. Patient should be instructed to not apply a double dose to make up for forgotten doses.

4.3 Contraindications

Tretinoin is contraindicated in patients with hypersensitivity to retinoids or to any ingredients contained in the preparation or component of the container.

4.4 4.4 Special Warnings and Precautions for use

Tretinoin is intended for external use only and should be kept away from areas of broken skin, lips, eyes, nose, mouth, and other mucous membranes because of its irritant effect. In case of accidental contact rinse well with water. In the case of the contact with the eye also refer the patient to an opthalmologist. If sensitivity or chemical irritation occurs, the medication should be discontinued.

Do not apply to eyelids or to the skin at the corners of the eyes and the mouth

Avoid the angles of the nose, skin fold areas and nasolabial fluids (if treatment in these areas is necessary, apply very sparingly with care not to let the medicines accumulate)

Topical use may induce severe local eryhtema and peeling at the site of application, If the degree of local irritation warrants, patients should be directed to use the medication less frequently, discontinue use temporarily or discontinue altogether.

Tretinoin cream should be used with caution in patients using medications that are known photosensitizers

Tretinoin cream has been reported to cause severe irritation of eczematous skin and should only be used with utmost caution in patients with this condtion

Tretinoin has irritant properties, hightens susceptibility to ultraviolet light radiation, is sensitive to oxidation and is photolabile

Tretinoin cream should be used with caution in patients with:

a history of local tolerability, reactions, photoallergy or local hypersensitivity

a personal or family history of skin cancer

inflammatory skin conditions that coexist with acne

sensitive skin and/or fair complexion

During early weeks of therapy, an apparent exacerbation of the acne lesions may occur due to an unexpected drug effect on previously unseen deep lesions. This is an anticipated therapeutic effect and therapy should be continued. Dosing frequency may be reduced or a lower strength of Tretinoin Cream may be used. If applicable to help prevent exacerbations of acne lesions

Skin: 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 in patients with inflammatory skin conditions that coexist with acne

The skin of certain sensitive individuals, particularly those with fair complexions, may become excessively red, edematous, blistered or crusted when exposed to Tretinoin Cream

If skin irritation (redness, peeling or discomfort) or effects of other acne or other treatments with irritating potential are present, this should be resolved before initiating treatment with Tretinoin Cream

Patients should be advised that excessive application will not improve efficacy, but may increase the risk of severe skin irritation. If severe irritatin occurs, interrupt dosing to allow the skin to recover, and to re-evaluate the dosing regimen with the patient

Environmental Factors

As tretinoin may cause increased sensitivity to ultraviolet radiation, exposure to sunlight and sun lamps should be avoided or minimised during the use of Tretinoin Cream. When exposure to strong sunlight cannot be avoided (eg. patients whose occupation require considerable exposure to the sun), patients should be advised to use a broad spectrum sunscreen with an SPF of atleast 15, to re apply sunscreen regularly and to wear protective clothing over treated areas.

Due to potential for photosensitivity, resulting in a greater rsik for sunburn, Tretinoin should be used with caution in patients with a personal or family history of skin cancer

If a patients has sunburn, this could be resolved before initiating treatment with Tretinoin Cream.

If sunburn occurs while using tretinoin cream it is advisable to interrupt therapy until the severe erythema and peeling subsides

Weather extremes such as wind or cold may be more irritating to patients using tretinoin containing products

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant applications 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 product should be applied at different times of the day (eg. one in the morning and one in the evening)

Augmented photosensitivity: Medications known to be photosensitisers (thiazides, tetracyclines, fluoroquinolones, phenothiazenes, sulphonamides) should be used with caution with Tretinoin Cream because augmented photosensitivity may occur.

Cumulative Irritation: Concomitant topical acne therapy and other topical medications should be used with caution because cumulative irritation may occur. Particular caution should be exercised during concomitant use of preparations containing a peeling agent (such as sulfur, resorcinol or salicylic acid) with tretinoin cream. If irritation or dermatitis occur (redness, peeling or discomfort) reduce frequency of application or temporarily interrupt treatment and resume once irritation subsides. Treatment should be discontinues if irritation persists

In patients whose skin has been subjected to procedures such as depilation, chemical hair treatments, chemical peels, dermaabrasion, or laser resurfacing allow the skin to recover before initiating the treatment with Tretinoin is considered

Cosmetics that have a strong drying effect, including products with high concetnrations of alcohol and/or astringents, or that have a potential irritating effect (abrasive agents, product containing spices or limes) should be used with caution as cumulative irritation may occur
Patients may use non comedogenic, hypoallergenic and oil-free cosmetic products

4.6 Pregnancy and lactation

Pregnancy

Topical tretinoin is not recommended during pregnancy or in women of childbearing potential without the proper use of an effective method of contraception

Nursing Women

It is not known whether tretinoin is excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the benefit of breastfeeding to the child and the benefit of the drug to the 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

If topical medication is applied excessively, marked redness, peeling or discomfort may occur. If severe irritation occurs, suspend treatment and appropritate symptomatic measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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. After administratioon, radioactivity was detected in samples of blood, urine stool on skin occlusive dressings

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

5.2 Pharmacokinetic properties

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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 ß-glucurono-g-lactone, respectively. Retinoyl ß-glucuronide was also identified in the liver and intestine.

5.3 Preclinical safety data

Carcinogenesis/Mutagenesis

In a carcinogenicity study in Fischer 344 rats given oral isotretinoin up to 32 mg/kg/day, there was an increased incidence of phaeochromocytomas relative to controls in both sexes at 32 mg/kg/day and in males at 8 mg/kg/day. Given the high rate of spontaneous rate of occurrence of phaeochromoyctoma in Fischer 344 rats, the relevance of this tumour to humans is uncertain.

Studies in hairless mice suggest that concurrent dermal exposure to isotretinoin at dose levels up to 500 mg/kg may enhance the tumorigenic potential of UV irradiation. The significance of these studies to humans is not clear.

The mutagenic potential of isotretinoin was evaluated in the Ames assay with and without S9 metabolic activation and in the Chinese hamster lung cell for chromosome aberrations, both of which were negative.

Reproductive Toxicology

Fertility

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dose levels of isotretinoin up to 32 mg/kg/day.

In dogs, testicular atrophy was noted after approximately 30 weeks at isotretinoin dose levels of 20 or 60 mg/kg/day. However, in studies of men receiving oral isotretinoin, no significant effects have been seen on semen parameters.

Pregnancy

Reproduction studies conducted in rabbits using isotretinoin gel applied topically at up to 60 times the human dose have revealed no harm to the foetus.

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

In one study, topical doses of a 0.1% ethanol solution, given to Wistar rats through gestational days (GDs) 6 to 16, were not tolerated at 10 mg/kg/day, causing severe local and systemic maternal toxicity. Offspring of dams receiving 5 mg/kg weighed significantly less than those of controls. Maternal toxicity (reduced weight gain and food consumption) was also evident at doses of 2.5 mg/kg/day or more. A significant increase in the occurrence of supernumerary ribs was observed at this dose, a result thought to be nonspecific or maternally mediated.

Topical administration of tretinoin at a dose of 10.5 mg/kg/day for 3 days to intact skin of hamsters on GDs 7, 8, and 9 resulted in erythema and/or epidermal hyperplasia at the site of application, but did not cause a significant teratogenic response.

Topical administration of 5 g 0.05% tretinoin ointment (corresponding to a dose of ~ 10 mg/kg) to the shaved backs of pregnant rats on GD 12 resulted in some retinoid-specific patterns of anomalies (humerus short 9%, radius bent 6%, ribs wavy 80%). This dose was ~100 fold that expected in humans.

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. REGISTRANT

Merit Organics Ltd

Plot No 2104/2/A, G.I.D.C , Sarigam , Bhilad,

Dist- Valsad-396155, Gujarat , INDIA

8. MANUFACTURER

Merit Organics Ltd

Plot No 2104/2/A, G.I.D.C , Sarigam , Bhilad,

Dist- Valsad-396155, Gujarat , INDIA

9. DATE OF REVISION OF THE TEXT

Applicable once the registration is obtained.