SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Isotrex 0.05% Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of cream contains 0.5 milligram of Isotretinoin (0.05% w/w).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream.

Description: A pale yellow cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Isotrex Cream is indicated for the topical treatment of mild to moderate acne vulgaris especially if comedones are predominant. The cream is particularly suitable for patients with dry skin.

4.2 Posology and method of administration

Adults and adolescents

Apply Isotrex Cream sparingly over the entire affected area once or twice daily, preferably after washing and drying the skin.

For patients with sensitive skin Isotrex Cream 0.05% is recommended. For other patients, Isotrex Cream 0.1% is recommended because of its greater effectiveness in treating comedonal acne and its quicker onset of action. If Isotrex Cream 0.1% causes irritation, Isotrex Cream 0.05% is recommended as an alternative.

If undue irritation (redness, peeling, or discomfort) occurs, patients should reduce frequency of application or temporarily interrupt treatment. The normal frequency of application should be resumed once the irritation subsides. Treatment should be discontinued if the irritation persists.

Patients should be advised that, in some cases, six to eight weeks of treatment may be required before the therapeutic effect is observed.

Patients should wash their hands after application of Isotrex Cream.

Patients should be advised that excessive application will not improve efficacy, but may increase the risk of skin irritation.

Use in Children

The safety and efficacy of topical isotretinoin in children prior to puberty have not been established, therefore isotretinoin is not recommended for use in this population.

Use in the Elderly

No specific recommendations as acne vulgaris rarely presents in the elderly.

4.3 Contraindications

Isotrex Cream should not be used in patients with known hypersensitivity to the active substance or to any of the ingredients.

Isotrex Cream is contraindicated in pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Contact with the mouth, eyes and mucous membranes and with abraded skin should be avoided.

Care should be taken not to let the medicine accumulate in skin fold areas and in the nasolabial folds.

Due to the irritant nature of Isotrex Cream, caution should be used when applying to sensitive areas of skin, such as the neck, or in patients with concomitant rosacea or perioral dermatitis. Isotrex should also be used with caution in patients who have had a problem tolerating this or similar retinoid products in the past.

Due to the potential for severe irritation, application to eczematous skin should be avoided.

Isotrex Cream should be used with caution in patients with a history of photoallergy.

As Isotrex Cream may cause increased sensitivity to sunlight, sunlamps should not be used and deliberate or prolonged exposure to sunlight should be avoided or minimised. When exposure to strong sunlight cannot be avoided, patients should be advised to use a sunscreen product and wear protective clothing. Due to the potential for photosensitivity, resulting in greater risk for sunburn, Isotrex Cream should be used with caution in patients with a personal or family history of skin cancer.

If a patient has sunburn, this should be resolved before using Isotrex Cream.

Concomitant topical acne therapy should be used with caution because a cumulative irritant effect may occur. If irritancy or dermatitis occur, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

Propylene glycol may cause skin irritation.

Cetostearyl alcohol may cause local skin reactions (e.g. contact dermatitis).

Chlorocresol may cause allergic reactions.

Butylated hydroxytoluene (BHT) may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant application of oxidising agents, such as benzoyl peroxide, should be avoided since they may reduce the efficacy of topical isotretinoin. If combination therapy is required, the products should be applied at different times of the day (eg, one in the morning and the other in the evening).

4.6 Fertility, pregnancy and lactation

Pregnancy

Topical isotretinoin is contraindicated during pregnancy and in women of childbearing potential unless an effective method of contraception is used during treatment. Treatment should be discontinued for one cycle prior to intended conception.

There are limited data available from the use of topical isotretinoin in pregnant women. However, studies totalling 1535 women exposed to topical tretinoin (an isomer of isotretinoin) in early pregnancy did not provide evidence of an increased risk of congenital abnormalities, including retinoic acid embryopathy or major structural defects.

In the clinical setting however, use of topical tretinoin in early pregnancy has been temporally associated with retinoic acid specific embryopathy. There are also a few reports of the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these reports in terms of risk to the foetus is uncertain, since no causal association has been established from these cases and these effects have not been reproduced.

Orally administered retinoids have been associated with congenital abnormalities. When used in accordance with the prescribing information, there is negligible systemic absorption from topically administered isotretinoin. However, risk cannot be excluded since there may be other factors that contribute to an increased systemic exposure.

Breastfeeding

There is insufficient information on the excretion of topically applied isotretinoin in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isotretinoin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of topical isotretinoin on fertility in humans, but isotretinoin in oral therapeutic dosages does not affect the number, motility, and morphology of sperm.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

The above adverse reactions, seen more frequently with the higher strength 0.1% cream, are generally moderate and usually subside with continued treatment.

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.

Not known: Skin hyperpigmentation, skin hypopigmentation, photosensitivity reaction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Oral ingestion of a 30 g tube of topical isotretinoin would result in less exposure than achieved with the recommended dosage of oral isotretinoin. Consequently, the theoretical occurrence of symptoms of overdosage (e.g. hypervitaminosis A) is highly unlikely.

Treatment

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: retinoids for topical use in acne, isotretinoin.

ATC Code: D10A D04

Mechanism of action

Isotretinoin is structurally and pharmacologically related to vitamin A, which regulates epithelial cell growth and differentiation. It is thought that topically applied isotretinoin acts in a comparable way to its stereoisomer, tretinoin, and:

- stimulates mitosis in the epidermis
- reduces intercelluar cohesion in the stratum corneum
- contests the hyperkeratosis characteristic of acne vulgaris
- aids desquamation, preventing the formation of lesions
- mediates an increased production of less cohesive epidermal sebaceous cells, which appears to promote the initial expulsion of comedones and their subsequent prevention.

Isotretinoin has topical anti-inflammatory actions. Topically applied isotretinoin inhibits leukotriene-B_4-induced migration of polymorphonuclear leukocytes, which accounts for topical isotretinoin's anti-inflammatory action. A significant inhibition was produced by topically applied isotretinoin but only a weak inhibition by topical tretinoin. This may account for the reduced rebound effect seen with topical isotretinoin when compared with topical tretinoin.

Pharmacodynamic effects

The pharmacological action of isotretinoin remains to be fully elucidated.

Isotretinoin binds to the 3 retinoic acid receptors (RAR) alpha, beta and gamma with less affinity and is unable to bind to retinoid X receptors (RXR) and the retinoic acid cellular receptor (CRABP).

There are studies which show similar activity to systemic actions when administered topically. Inhibition of sebum production by topical isotretinoin has been demonstrated in the ears and flank organs of the Syrian hamster. Application of isotretinoin to the ear for 15 days led to a 50% reduction in sebaceous gland size, and application to the flank organ resulted in a 40% reduction. Topical application of isotretinoin has also been shown to have an effect on the epidermal differentiation of rhino mouse skin. Reduction in the size of the utriculi or superficial cysts leading to normal looking follicles was a predominant feature of isotretinoin treatment and has been used to quantify the antikeratinising effects of isotretinoin.

5.2 Pharmacokinetic properties

Absorption

Percutaneous absorption of isotretinoin cream is negligible.

In a maximised study of the absorption of isotretinoin, daily application of 10 g 0.1% w/w isotretinoin cream for 42 consecutive days in patients with photodamaged skin resulted in only slightly elevated isotretinoin concentrations. Levels remained less than 2 ng/mL compared to baseline levels of approximately 1.2 ng/mL. Although a 48% increase in the mean isotretinoin plasma area under the curve (AUC_{24hr}) occurred, this elevation is less than that found after a daily allowance of vitamin A supplementation.

Applying ^{14}C-isotretinoin in a cream base on the healthy skin of human volunteers resulted in 0.03% of the topically applied dose being recovered through estimating the radioactivity of blood, urine and faecal samples.

Distribution

Systemic (oral) isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism

In vivo studies in humans showed that the three major metabolites identified in human plasma following systemic (oral) administration of isotretinoin were 4-oxo-isotretinoin, retinoic acid (tretinoin), and 4-oxo-retinoic acid (4-oxo-tretinoin). *In vitro* studies indicated that all of these metabolites had retinoid activity.

In vitro studies indicate that the major enzymes responsible for isotretinoin metabolism are cytochrome P450 isoenzymes 2C8, 2C9, 3A4 and 2B6. Isotretinoin and its metabolites are further metabolized into conjugates and excreted in urine and faeces.

Elimination

Following systemic (oral) administration of an 80 mg dose of ^{14}C-isotretinoin, radioactivity in the blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately eliminated in the faeces and urine in similar amounts (total of 65% to 83%).

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

Light Liquid Paraffin
Di-n-Butyl Adipate
Macrogolstearylether
Propylene Glycol
Cetostearyl Alcohol
Benzyl Alcohol
PEG-5 Glyceryl Stearate
Carbomer
Chlorocresol
Sodium Hydroxide
Butylated Hydroxytoluene (BHT)
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

a) For the product packaged for sale

Two years

b) After first opening the container

Comply with expiry date

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Internally lacquered membrane-sealed aluminium tubes fitted with a polyethylene screw-cap, packed into a carton. Pack size: 15, 25, 30, 40 and 50 grams.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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