IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0144/031/003
Case No: 2040720

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Stiefel Labs (U.K.) Ltd.

Holtspur Lane, **Wooburn Green**, **High Wycombe**, **Bucks HP10 0AU**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Isotrex Cream 0.10%

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/10/2007** until **01/10/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isotrex Cream 0.10%

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isotretinoin 0.1% w/w.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Cream
Pale yellow cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ISOTREX CREAM is indicated for the topical treatment of mild to moderate acne vulgaris and is effective in treating both inflammatory and non-inflammatory lesions. The cream is particularly suitable for patients with sensitive or dry skin.

4.2 Posology and method of administration

Adults

Apply ISOTREX CREAM sparingly over the entire affected area once or twice daily.

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

Use in Children

Not established for prepubescent children, in whom acne vulgaris rarely presents.

Use in the Elderly

No specific recommendations as acne vulgaris does not present in the elderly.

4.3 Contraindications

ISOTREX CREAM should not be used in patients with known hypersensitivity to any of the ingredients.

4.4 Special warnings and precautions for use

Contact with the mouth, eyes and mucous membranes and with abraded or eczematous skin should be avoided. Application to sensitive areas of skin, such as the neck, should be made with caution. As ISOTREX CREAM may cause increased sensitivity to sunlight, deliberate or prolonged exposure to sunlight or sunlamps should be avoided or minimised. Concomitant topical medication should be used with caution because a cumulative irritant effect may occur.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Category B1.

The safety of ISOTREX CREAM for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or foetus, the course of gestation and peri- and post-natal development.

Isotretinoin has been associated with teratogenicity in humans when administered systemically. However, reproduction studies conducted in rabbits using topical isotretinoin applied at up to 60 times the human therapeutic dose have revealed no harm to the foetus.

The use of ISOTREX CREAM should be avoided by women who are pregnant or intending to conceive.

Use during Lactation

Percutaneous absorption of isotretinoin from ISOTREX CREAM is negligible. However, as it is not known if isotretinoin is excreted in human milk, ISOTREX CREAM should not be used during lactation.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

ISOTREX CREAM may cause slight stinging, burning or irritation; erythema and peeling at the site of application may occur. These local effects are generally moderate and usually subside with continued treatment. If undue irritation occurs, treatment should be interrupted temporarily and resumed once the reaction subsides. If irritation persists, treatment should be discontinued. Reactions will usually resolve on discontinuation of therapy.

4.9 Overdose

Acute overdosage of ISOTREX CREAM has not been reported to date. Isotretinoin is not expected to cause problems on ingestion of the topical cream.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Isotretinoin is structurally and pharmacologically related to vitamin A, which regulates epithelial cell growth and differentiation. The pharmacological action of isotretinoin has not been fully determined. When used systemically, it suppresses sebaceous gland activity and reduces sebum production; it also affects comedogenesis, inhibits follicular keratinisation, suppresses *Propionibacterium acnes* and reduces inflammation. It is thought that topically applied isotretinoin stimulates mitosis in the epidermis and reduces intercellular cohesion in the stratum corneum; contests the hyperkeratosis characteristic of acne vulgaris and aids desquamation, preventing the formation of lesions. It is also thought that it mediates an increased production of less cohesive epidermal sebaceous cells. This appears to promote the initial expulsion and subsequent prevention of comedones.

Studies in animal models have shown similar activity when isotretinoin is applied 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.

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.

5.2 Pharmacokinetic properties

Percutaneous absorption of isotretinoin from ISOTREX CREAM is negligible. In a maximised study of the absorption of isotretinoin from ISOTREX CREAM 0.1% w/w in patients suffering from widespread acne, levels were shown to be only slightly raised from baseline levels (isotretinoin is normally present in plasma). Levels remained less than 5ng/ml. Applying 14C isotretinoin in a cream base on the healthy skin of volunteers resulted in only 0.03% of the topically applied dose being recovered through estimating the radioactivity of blood, urine and faecal samples.

5.3 Preclinical safety data

Isotretinoin is a well-established pharmacopoeial substance which is regularly used in the topical and systemic treatment of acne vulgaris. Preclinical safety studies have not been conducted on ISOTREX CREAM, as an extensive range of toxicological studies has been conducted on isotretinoin itself and the topical gel formulation. Human patch tests for irritation (repeat insult patch test) and sensitisation have demonstrated the acceptability of the cream formulation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Light liquid paraffin
Di-n-Butyl Adipate
Polyoxyethylene stearyl ether
Propylene glycol

Cetostearyl alcohol
Benzyl alcohol
PEG-5 glyceryl stearate
Carbomer 940
Chlorocresol
Sodium hydroxide
Butylated hydroxytoluene (BHT)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

Internally lacquered membrane-sealed aluminium tubes fitted with a plastic screw-cap, packed into a carton. Pack sizes: weight from 25 to 50 grammes.

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

Stiefel Laboratories (UK) Ltd
Holtspur Lane
Wooburn Green
High Wycombe
Bucks HP10 0AU
England

8 MARKETING AUTHORISATION NUMBER

PA144/31/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 October 1998

Date of last renewal: 02 October 2003

10 DATE OF REVISION OF THE TEXT

September 2004