**PRODUCT DESCRIPTION**
Topical gel contains Isotretinoin 0.05 % w/w (0.05 g per 100 g gel).
Topical cream contains Isotretinoin 0.05 % w/w (0.05 g per 100 g cream).

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

**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 intercellular 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, which are mediated by the inhibition of leukotriene-B4-induced migration of polymorphonuclear leukocytes. 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. It has the following actions when given systemically:
- suppresses sebaceous gland activity
- reduces sebum production
- prevents or reduces comedogenesis
- suppresses *Propionibacterium acnes*
- reduces inflammation.

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; 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 (which contain areas of sensory epithelium in the ears) 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.

**Pharmacokinetics**

**Absorption**

**Topical Gel**
Following Isotretinoin 0.05% gel application to acne patients at a daily dose of 20 g (equivalent to 10 mg of Isotretinoin) to the face, chest and back for 30 days, plasma concentrations of Isotretinoin and Tretinoin were not measurable (< 20 ng/mL).

**Topical Cream**
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 (AUC24h) occurred, this elevation is less than that found after a daily allowance of vitamin A supplementation.

Applying 14C-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**
Orally-administered 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 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 oral administration of an 80 mg dose of 14C-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%).

**Special patient populations**
- **Children**
  Not relevant for this product.
- **Elderly**
  Not relevant for this product.
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 some retinoid-specific patterns of anomalies (humerus short 9%, radius bent 6%, ribs wavy 80%). This dose was ~100 fold that expected in humans.

In one study, topical doses of a 0.1% ethanol solution, given to Wistar rats through gestational days (GDs) 6 to 16, were 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 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.

The mutagenic potential of Isotretinoin was evaluated in mice exposed to UV radiation. The significance of these studies to humans is not clear. The reproductive 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.

Non-clinical information

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 phaeochromocytoma 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 gonad 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 embryofetal 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 non-specific 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.

INDICATIONS

Isotretinoin (IsotreX®) is indicated for the treatment of mild to moderate acne vulgaris.

DOSAGE AND ADMINISTRATION

• Adults and adolescents

Isotretinoin (IsotreX®) should be applied sparingly over the affected area once or twice daily, preferably after washing and drying the skin.

Hands should be washed after application.

6-8 weeks of treatment may be required before a therapeutic effect is observed.

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

Topical Gel

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.

Topical Cream

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 and resumed once the irritation subsides. Treatment should be discontinued if the irritation persists.

CONTRAINDICATIONS

Isotretinoin (IsotreX®) should not be used in patients with known hypersensitivity to any of the ingredients.

WARNINGS AND PRECAUTIONS

Isotretinoin (IsotreX®) should be used with caution in patients with a history of local tolerability reactions or photoallergy.

Use with caution in patients with a personal or family history of skin cancer.

Contact with the mouth, eyes, mucous membranes, abraded or eczematous 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 Isotretinoin, caution should be used when applying to sensitive areas of skin, such as the neck, or in patients with concomitant rosacea or perioral dermatitis.

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

Sensitivity to sunlight

As Isotretinoin 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.
Effects on Ability to Drive and Use Machines
With only negligible percutaneous absorption of Isotretinoin from topical preparations, no detrimental effects on such activities are predicted from the adverse reaction profile of topical Isotretinoin.

DRUG INTERACTIONS
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).

PREGNANCY AND LACTATION
Fertility
There are no data on the effect of topical Isotretinoin (Isotrexa®) on fertility in humans, but Isotretinoin in oral therapeutic dosages does not affect the number, motility, and morphology of sperm (see Non-clinical Information).

Pregnancy
Studies totalling almost 1600 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 overall. A small number of temporally associated congenital abnormalities have been reported during clinical use of topical Tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, they include 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 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 such as:
- amount used
- skin barrier integrity
- concurrent use with other products
- dietary intake of or ingestion of supplements containing vitamin A.

Therefore, topical Isotretinoin is not recommended during pregnancy or in women of childbearing potential not using an effective method of contraception properly. No specific contraceptive precautions are necessary for men using topical Isotretinoin.

Lactation
There is insufficient information on the excretion of topically applied Isotretinoin in human milk. A risk to the newborn/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.

ADVERSE EFFECTS
The following convention is used for the classification of the frequency of an adverse reaction and is based on the CIOMS guidelines:
- Very common: ≥1/10
- Common: ≥1/100 to <1/10
- Uncommon: ≥1/1000 to <1/100
- Rare: ≥1/10000 to <1/1000
- Very rare: <1/10000
- Not known*: (cannot be estimated from the available data)

Clinical trial data
Skin and subcutaneous tissue disorders

Topical Cream
- Application site erythema, skin exfoliation, pain of skin, application site pruritus, skin irritation, skin tenderness, skin burning sensation, application site stinging, dry skin

Post-marketing data
Skin and subcutaneous tissue disorders

Rare: skin hyperpigmentation, skin hypopigmentation, photosensitivity reaction

OVERDOSAGE AND TREATMENT
Symptoms and signs
Oral ingestion of a 30g 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 overdose (e.g. hypervitaminosis A) is highly unlikely.

Topical Gel
The gel formulation contains more than 95% ethanol. Systemic absorption of this should be considered in the event of oral ingestion.

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

STORAGE CONDITION
Isotretinoin (Isotrexa®) Cream: Store at temperatures not exceeding 30°C.
Isotretinoin (Isotrexa®) Gel: Store at temperatures not exceeding 30°C.
AVAILABILITY
Isotretinoin (Isotrexa®) Cream: Aluminum tube of 40g. Box of 1’s
Isotretinoin (Isotrexa®) Gel: Aluminum tube of 10g and 30g. Box of 1’s

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

ISOTREX is a trademark of Stiefel Laboratories Inc.

Version number: GDS02       Revision date: 4 April 2011

GlaxoSmithKline

Imported by:
GlaxoSmithKline Philippines Inc
2266 Chino Roces Avenue, City of Makati
Tel. 892-0761

Mfd by:
Stiefel Laboratories (Pte) Ltd
103 Gul Circle, Singapore