Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isotrex 0.5 mg/g Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of gel contains 0.5 mg of isotretinoin.

Excipients with known effects:
Contains butylated hydroxytoluene (E321) 0.1 mg/g.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel
A soft, greenish yellow gel with an odour of ethanol

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Isotrex Gel is indicated for the topical treatment of mild to moderate inflammatory and non-inflammatory acne vulgaris.

4.2 Posology and method of administration

Adults and adolescents
Apply Isotrex Gel sparingly over the whole affected area once or twice daily.

Patients should be advised that 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.

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.

Hands should be washed after application.

Due to the flammable nature of Isotrex Gel, patients should avoid smoking or being near an open flame during application and immediately after use.

Paediatric population
The safety and efficacy of Isotrex Gel in children under 12 years of age has not been established since acne vulgaris rarely presents in this age group.

Elderly patients
There are no specific recommendations for use in the elderly. Acne vulgaris does not present in the elderly.

4.3 Contraindications

Hypersensitivity to the active substance, isotretinoin, or to any of the excipients listed in section 6.1. Isotrex Gel is contraindicated in pregnancy and in women planning a pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Isotretinoin 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.

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

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 occur, reduce frequency of application or temporarily interrupt treatment and resume once the irritation subsides. Treatment should be discontinued if the irritation persists.

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.

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 (e.g. one in the morning and the other in the evening).

4.6 Fertility, pregnancy and lactation

Pregnancy

Isotrex Gel is contraindicated in pregnancy, or in women planning a pregnancy (see section 4.3). If the product is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.

Studies totaling 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, topically administered retinoids are generally assumed to result into low systemic exposure due to minimal dermal absorption. However, there could be individual factors (e.g. damaged skin barrier, excessive use) that contribute to an increased systemic exposure.

No specific contraceptive precautions are necessary for men using topical isotretinoin.

Breast-feeding
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

Isotrex has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In normal use, Isotrex Gel may cause stinging, burning or irritation; erythema and peeling at the site of application may occur.

If undue irritation occurs, treatment should be interrupted temporarily and resumed once the reaction subsides. If irritation persists, treatment should be discontinued. Reactions will normally resolve on discontinuation of therapy.

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

Very common: 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

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
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 overdosage (e.g. hypervitaminosis A) is highly unlikely. These include severe headaches, nausea or vomiting; drowsiness, irritability and pruritus.

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

Management
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.
ATC code: D10AD04.

Isotretinoin is structurally and pharmacologically related to Vitamin A which regulates epithelial cell growth and differentiation.

The pharmacological action of isotretinoin remains to be fully elucidated. When used systemically it suppresses sebaceous gland activity and reduces sebum production; it also affects comedogenesis, suppresses Propionibacterium acnes and reduces inflammation.

When applied topically, the mode of action of isotretinoin is probably comparable with its stereoisomer, tretinoin. Tretinoin stimulates mitosis in the epidermis and reduces intercellular cohesion in the stratum corneum; it contests the hyperkeratosis characteristic of acne vulgaris and aids desquamation, preventing the formation of lesions. Tretinoin also mediates an increased production of less cohesive epidermal sebaceous cells, this appears to promote the initial expulsion and subsequent prevention of comedones.

Animal studies have demonstrated that topical isotretinoin elicits epidermal hyperplasia reduces hyperkeratosis and suppresses sebum production and sebaceous gland size. The anti-inflammatory action of isotretinoin when applied topically has been confirmed in man.

5.2 Pharmacokinetic properties

Percutaneous absorption of isotretinoin from the gel is negligible. After applying 20g per day of isotretinoin 0.05% gel to acne of the face, chest and back for 30 days, HPLC assays for isotretinoin and tretinoin demonstrated non-detectable levels in the plasma samples (<0.02μg/ml). Applying ^{14}C 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

The relevant information is given in Section 4.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene (E321)
Hydroxypropylcellulose
Ethanol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 3 years
Once opened: use within 2 months after opening the tube and discard any unused portion.

6.4 Special precautions for storage

Store below 25^{o}C. Replace cap securely after use.
Contents are flammable. Keep away from fire, flame or heat. Do not leave in direct sunlight.

6.5 Nature and contents of container

Internally lacquered membrane-sealed aluminium tubes fitted with a polyethylene screw-cap, packed into a carton. Pack contents: 30 g.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA1077/122/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 1992

Date of last renewal: 18 August 2007

10 DATE OF REVISION OF THE TEXT

August 2018