Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Isotrexin 20 mg/g + 0.5 mg/g Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Erythromycin	20 mg/g
Isotretinoin	0.5 mg/g

Excipients with known effect:
butylated hydroxytoluene (E321) 0.1mg/g.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel
Pale yellow soft gel with an odour of ethanol.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Isotrexin is indicated for the topical treatment of mild to moderate acne vulgaris in adults and children over 12 years of age.

4.2 Posology and method of administration

Isotrexin is for topical use only.

Adults & children over 12 years
Wash the skin gently with a mild cleanser and dry fully. Apply Isotrexin in a thin film over the entire affected area once or twice daily. Avoid close proximity to eyes, lips, and other mucous membranes. Hands should be washed after application.

8 weeks of treatment may be required before a therapeutic effect is observed. The efficacy and safety of Isotrexin has not been studied beyond 12 weeks in acne vulgaris clinical trials. The prescriber should evaluate the benefit of continuing treatment beyond 12 weeks of uninterrupted use, taking account of an increased risk of antimicrobial resistance.

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 may use a moisturizer as needed and 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. Efficacy has not been established for less than once daily dosing frequencies.

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

Paediatric population
The safety and efficacy of Isotrexin has not been established in children less than 12 years of age, therefore Isotrexin is

not recommended for use in this population.

Use in the Elderly
There are no specific recommendations for use in the elderly.

Renal impairment
No dosage adjustment is necessary.

As there is low systemic absorption of isotretinoin and erythromycin following topical application, renal impairment is not expected to result in systemic exposure of clinical significance. .

Hepatic impairment
No dosage adjustment is necessary.

As there is low systemic absorption of isotretinoin and erythromycin following topical application, hepatic impairment is not expected to result in systemic exposure of clinical significance. .

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. Isotrexin is contraindicated in pregnancy and in women planning a pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Local tolerability and photoallergy reactions
Isotrexin should be used with caution in patients with a history of local tolerability reactions or photoallergy.

Irritancy
Contact with the mouth, eyes, lips, other mucous membranes or areas of broken skin should be avoided. In case of accidental contact, rinse well with water. Care should be taken not to let the medicine accumulate in skin folds.

Due to the irritant nature of isotretinoin, caution should be used when applying to sensitive areas of the skin, such as the neck, abraded or eczematous skin, or when treating patients with inflammatory skin conditions that may coexist with acne, e.g. 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.

In patients whose skin has been subjected to procedures such as depilation, chemical hair treatments, chemical peels, dermabrasion or laser resurfacing, the skin should be allowed to recover before application is considered.

Cosmetics that have a strong drying effect, including products with high concentrations of alcohol and/or astringents, or that have a potential irritating effect should be used with caution as a cumulative irritant effect may occur.

Resistance to erythromycin
The treatment of acne with topical antibiotics is associated with the development of antimicrobial resistance in *Propionibacterium acnes* as well as other bacteria (e.g. *Staphylococcus aureus, Streptococcus pyogenes*). The use of erythromycin may result in resistance developing in these organisms.

If there is evidence of the development of clinical resistance during treatment (e.g. poor response or worsening of the condition), treatment with Isotrexin should be discontinued.

Cross-resistance
Cross-resistance with other antibiotics of the macrolide group and with clindamycin may occur (see section 4.5).

The use of antibiotic agents may be associated with the overgrowth of antibiotic-resistant organisms. If this occurs, discontinue use.

Pseudomembranous colitis
Isotrexin should be used with caution in patients with or with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis (including pseudomembranous colitis).

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. Although this is less likely to occur with topically applied Isotrexin, if prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Sensitivity to sunlight and environmental exposure
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 broad-spectrum sunscreen product (protects against UVA and UVB rays) and wear protective clothing. Due to the potential for photosensitivity, resulting in greater risk for sunburn, Isotrexin 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 Isotrexin.

Weather extremes, such as wind or cold, may be more irritating to patients using isotretinoin-containing products.

Isotrexin contains butylated hydroxytoluene which 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

No formal drug-drug interaction studies have been conducted with Isotrexin.

Isotrexin should not be used in combination with clindamycin-containing products due to possible antagonism to the clindamycin component.

Concomitant application of oxidising agents, such as benzoyl peroxide, should be avoided since they may reduce the efficacy topical isotretinoin. If combination therapy is required, they 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
Isotrexin 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.

There are limited data on the use of Isotrexin in pregnant women.

Erythromycin
There are limited data on the use of topical erythromycin in pregnant women. No effects during pregnancy are anticipated since systemic exposure to erythromycin is very low (see section 5.2).

Isotretinoin
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.

A number of observational studies of varying sample size involving a total of 1535 women exposed to topical tretinoin (an isomer of isotretinoin) in early pregnancy did not provide evidence of an increased risk of congenital abnormalities.

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.

No specific contraceptive precautions are necessary for men using Isotrexin.

Breast-feeding
Isotrexin has not been studied during breast-feeding.

Percutaneous absorption of erythromycin is low; however, it is not known whether erythromycin is excreted in human milk after topical application. Erythromycin is excreted in human milk following oral and parenteral administration.

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 Isotrexin 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 Isotrexin (or the topical single actives) on fertility in human, but isotretinoin in oral therapeutic dosages does not affect the number, motility and morphology of sperm (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse drug reactions (ADRs) are summarised below for Isotrexin as a combination and include any additional ADRs that have been reported for the single topical active ingredients, erythromycin or isotretinoin.

Adverse drug reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000).

MedDRA SOC	**Very Common**	**Common**	**[1]Rare**
Immune system disorders			Allergic reaction
Gastrointestinal disorders			Abdominal discomfort, abdominal pain upper, diarrhoea
Skin and subcutaneous tissue disorders	Rash, [2]dryness, [2]erythema, [2]scaling, [2]burning, [2]pruritus [3]skin irritation		Photosensitivity reaction, skin discolouration, skin hyperpigmentation, skin hypopigmentation, urticaria
General disorders and	Pain	Application site reactions	Facial oedema

Administration site conditions		including eczema, exfoliative dermatitis	

[1]Based on post-marketing reports.

[2]Reported from local tolerability assessments during a 12 week clinical study.

[3]Reported from clinical studies conducted with topical erythromycin and topical isotretinoin.

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
In the event of accidental ingestion, gastrointestinal adverse reactions similar to those following orally administered erythromycin may be seen (e.g. nausea, vomiting, diarrhoea).

Oral ingestion of a 50g tube of Isotrexin 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.

The formulation contains a significant quantity of ethanol. Systemic absorption of this should be considered a possibility in the event of overdosage.

Treatment
Appropriate symptomatic measures should be taken to provide relief from skin irritation due to excessive application.

Accidental ingestion should be managed 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 combinations.
ATC code: D10AD54

Mechanism of action

Isotretinoin
Isotretinoin is the 13-cis-isomer of all-trans-retinoic acid. It 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, by:

- stimulating mitosis in the epidermis
- reducing intercellular cohesion in the stratum corneum and eliminating mature comedones (closed and open)
- contesting the hyperkeratosis characteristic of acne vulgaris by suppressing the formation of micromedo
- preventing the formation of lesions through inflammatory process inhibition
- mediating an increased production of less cohesive sebaceous cells, which appears to promote the initial expulsion of comedones and their subsequent prevention
- Facilitating percutaneous absorption when co-administered with other topical drugs

Isotretinoin has topical anti-inflammatory actions, which are mediated by the inhibition of leukotriene-B_4-induced migration of polymorphonuclear leukocytes. The migration of LTB4 into human skin is significantly inhibited by topically applied isotretinoin.

Erythromycin
Erythromycin is a macrolide antibiotic with a broad and essentially bacteriostatic action against many Gram-positive and to a lesser extent Gram-negative bacteria. Erythromycin binds reversibly to the 50S subunit of the bacterial ribosome, blocking the formation of peptide bonds between amino acids thus inhibiting protein synthesis and cell growth in susceptible organisms. Depending on the organism and dose administered, erythromycin exhibits either bacteriostatic or bactericidal activity.

Applied topically, erythromycin suppresses *Propionibacterium acnes*, resident bacteria of sebaceous follicles, thus reducing the *P. acnes* mediated hydrolysis of triglycerides to fatty acids and therefore decreasing fatty acid formation. Erythromycin has also demonstrated inhibitory effects on the production of *P. acnes*-associated inflammatory mediators. Therefore, it also works to control acne lesion counts by direct antibacterial effects and indirect anti-inflammatory effects.

Pharmacodynamic effects

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

Erythromycin
The exact mechanism by which erythromycin reduces lesions of acne vulgaris is not fully known. However, the effect appears to be due in part to the antibacterial activity of the drug and to the anti-inflammatory effects of erythromycin.

Resistance and cross-resistance
The treatment of acne with topical antibiotics used as monotherapy has been associated with the development of antimicrobial resistance in *Propionibacterium acnes* as well as commensal flora (e.g. *S. aureus, S. pyogenes*). The use of erythromycin may result in developing inducible or constitutive resistance in these organisms.

Cross-resistance can develop as a result of point mutations in the genes encoding the 23S ribosomal RNA. As a result of these point mutations, most strains of *P acnes* that are resistant to erythromycin may be cross-resistant to clindamycin.

The prevalence of acquired resistance may vary geographically and with time for selected organisms. Local information on resistance is desirable.

Clinical Studies
The safety and efficacy of Isotrexin (applied twice daily) were evaluated in a 12-week double-blind, randomised, placebo-controlled, parallel group, study in 161 patients aged 16-32 years with mild to moderate acne vulgaris. Isotrexin was compared with erythromycin 20 mg/g in a vehicle gel, isotretinoin 0.5 mg/g in a vehicle gel and a vehicle gel alone.

Efficacy was assessed by comparison between the groups of the total number of lesions (combined inflammatory and non-inflammatory), total number of inflammatory lesions, total number of non-inflammatory lesions and acne severity grade. Global change scores (investigator assessment) and the patient's self-rating assessment of their condition were also evaluated. The findings are presented in the table below.

Changes from baseline to week 12 in lesion counts and acne severity grade

	Isotrexin (N=40)	**Erythromycin (20 mg/g)** (N=41)	**Isotretinoin (0.5 mg/g)** (N=40)	**Vehicle Gel (Placebo)** (N=40)
Inflammatory Lesions				
Mean reduction from baseline	-16.3	-10.9	-8.1	-6.9

±SD	22.9	12.4	16.2	20.0
P-value compared with Erythromycin/isotretinoin		0.213	0.060	0.032
Non-Inflammatory Lesions				
Mean reduction from baseline	-18.9	-13.2	-16.9	-6.4
±SD	26.5	19.5	26.8	23.4
P-value compared with Erythromycin/isotretinoin		0.323	0.727	0.031
Total Lesions (inflammatory and non-inflammatory)				
Mean reduction from baseline	-35.2	-24.0	-25.0	-13.4
±SD	45.1	25.3	33.7	36.6
P-value compared with Erythromycin/isotretinoin		0.190	0.232	0.012
Acne Severity Grade				
Mean reduction from baseline	-0.31	-0.20	-0.17	-0.23
±SD	0.37	0.22	0.32	0.28
P-value compared with Erythromycin/isotretinoin		0.144	0.054	0.223

All statistical tests were 2-tailed and performed at the 5% level of significance (p=0.05).
Analysis of variance was used to compare the 4 treatment groups for changes of week 4, 8 and 12 from baseline.

Isotrexin gave the greatest improvement for all acne assessments at week 12. Isotrexin significantly ($p<0.05$) reduced the mean total lesions (inflammatory and non-inflammatory) when compared with placebo.

For investigator assessments of global change, a greater proportion of subjects in the Isotrexin group showed improvement relative to the other 3 groups at weeks 8 and 12. Similar numbers of patients claimed their condition had improved with Isotrexin or isotretinoin and they were deemed more efficacious than erythromycin or placebo when observed at Week 12.

5.2 Pharmacokinetic properties

Absorption
Studies support the conclusion that systemic absorption of erythromycin and isotretinoin from topical application of Isotrexin is low and is not different from that of drug products containing the individual drug substances.

The plasma levels of erythromycin, isotretinoin and its metabolites from topically applied gel (isotretinoin (0.05%), erythromycin (2.0%) and in combination) were measured in 2 studies conducted in acne patients. The first study, an open, follow-up study to the 12 week pivotal study, measured the plasma levels of the actives in 24 subjects with mild to moderate acne over 4 weeks. The subjects applied the gel with a mean of 0.652 g ±0.871 g per application. The second study enrolled 51 subjects with moderate to severe acne and measured the absorption after maximum application of the gel to an extensive area of acne vulgaris (mean value of 2.078 g per application) twice daily for 4 weeks.

Both studies demonstrated that the absorption of isotretinoin and erythromycin was low. Systemic concentrations from topical application of isotretinoin were less than 2 ng/mL, or within the natural endogenous levels of isotretinoin of 0.5 to 5 ng/mL. Likewise, topically applied erythromycin does not appear to be absorbed through the skin (no quantifiable levels of erythromycin were obtained from any of the samples assayed). Combining isotretinoin and erythromycin in the gel formulation does not affect the absorption characteristics of the individual drug substances.

Distribution
Distribution of erythromycin or isotretinoin throughout the body after topical application has not been considered, as there is no evidence that the compounds are absorbed to any measurable extent after being applied to the skin.

Erythromycin is about 65% bound to plasma proteins, primarily to alpha 1 acid glycoprotein (approximately 55%).

Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism
No data exist relating to the metabolism, if any, of erythromycin on the skin. After systemic administration, erythromycin is inactivated in the liver by demethylation of the d−desosamine group, a reaction catalyzed by cytochrome P450 IIA.

Very little data exist describing the metabolism of isotretinoin after topical applications to human skin. Isotretinoin may be metabolized by cytochrome P450 enzymes or other endogenous oxidative agents and radicals in the skin.

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 showed that the major enzymes responsible for isotretinoin metabolism are cytochrome P450 isoenzymes 2C8 and 3A4.

Elimination
Topically applied erythromycin or isotretinoin is unlikely to reach systemic circulation in measurable quantities. If very small quantities of erythromycin or isotretinoin are absorbed, they will be oxidised and excreted in bile or in urine, respectively.

5.3 Preclinical safety data

Carcinogenesis/mutagenesis
No carcinogenicity or genotoxicity studies were conducted with Isotrexin gel.

Erythromycin
Carcinogenicity studies have not been conducted with erythromycin base.

Carcinogenicity studies in mice and rats with dietary administration of erythromycin stearate did not show evidence of tumorigenicity.

Genotoxicity studies have not been conducted with erythromycin base.

Erythromycin stearate was not mutagenic in a bacterial mutagenicity assay (*Salmonella typhimurium*) in the presence and absence of metabolic activation, and was not genotoxic in a chromosome aberration assay and a sister chromatid exchange assay in Chinese Hamster Ovary cells, in the presence and absence of metabolic activation. A small increase in mutation frequency of questionable biological relevance was observed in the mouse L5178Y lymphoma cell assay in the absence of metabolic activation.

Isotretinoin
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.

Isotretinoin was negative for mutagenicity *in vitro* in the Ames, chromosomal aberration, and unscheduled DNA synthesis assays and *in vivo* in the mouse micronucleus assay.

Reproductive Toxicology

Fertility
No fertility and early embryonic development studies have been conducted with Isotrexin gel.

Erythromycin
There are no data on the effect of topical erythromycin on fertility.

Isotretinoin
No adverse effects on gonadal function, fertility, conception rate, gestation, parturition, neonatal viability, or lactation were observed at oral doses of isotretinoin up to 32 mg/kg/day in rats. In dogs, testicular atrophy and depression of spermatogenesis were observed after 30 weeks of 20 or 120 mg/kg/day isotretinoin treatment.

Pregnancy
No embryo-foetal development studies have been conducted with Isotrexin gel.

Erythromycin
There are no data on the effect of topical erythromycin on embryo-fetal development.

Isotretinoin
A teratology study conducted in New Zealand White rabbits administered isotretinoin gel topically at up to 60 times the human dose revealed no evidence of embryotoxicity or teratogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylcellulose
Butylated Hydroxytoluene (E321)
Ethanol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25˚C.
Keep container tightly closed when not in use.
Contents are flammable. Keep away from fire, flame or heat.
Replace cap firmly after use to prevent evaporation.
Do not leave Isotrexin in direct sunlight.

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: 6, 25, 30, 40, and 50 grams.

Not all pack sizes may be marketed in Ireland.

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

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

8 MARKETING AUTHORISATION NUMBER

PA1077/123/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 02 October 2008

10 DATE OF REVISION OF THE TEXT

August 2018