

PRODUCT INFORMATION

ISOTREX® GEL

NAME OF THE MEDICINE

Isotretinoin.

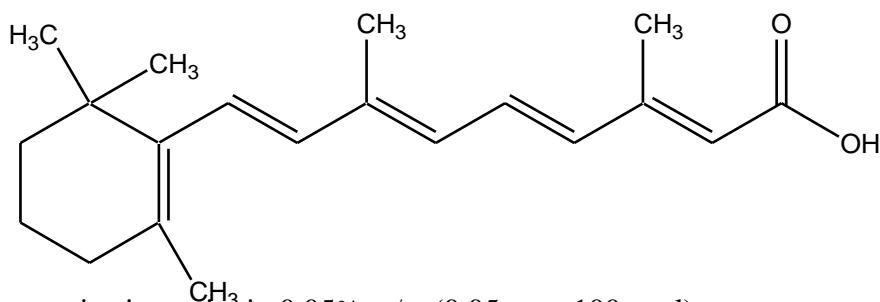
DESCRIPTION

Isotretinoin is a yellow to orange crystalline powder; it has the following chemical structure:

Chemical name: 13-cis-retinoic acid; 3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-cis-4-trans-6-trans-8-trans-nonatetraenoic acid.

CAS Number: 4759-48-2.

Molecular formula: C₂₀H₂₈O₂. Molecular weight: 300.44.



Isotrex gel contains isotretinoin 0.05% w/w (0.05g per 100g gel).

Excipients are butylated hydroxytoluene, hydroxypropylcellulose and ethanol.

PHARMACOLOGY

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 shows significant inhibition of leukotriene-B₄-induced migration of polymorphonuclear leukocytes, which may contribute to its topical anti-inflammatory activity. Only a weak inhibition of polymorphonuclear leukocyte migration is produced 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*, and
- 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. Topical application of isotretinoin has also been shown to have an effect on the epidermal differentiation of rhino mouse skin, resulting in a reduction in the size of the utriculi and superficial cysts which are hair follicle-derived squamous epithelium containing keratin, a feature of the skin of this animal model.

Pharmacokinetics

Absorption

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).

Distribution

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 and 3A4 with additional smaller roles for 3A7, 4A11, 1B1, 2B6 and 2C19. Isotretinoin and its metabolites are further metabolized into conjugates and excreted in urine and faeces.

INDICATIONS

Isotrex gel is indicated for the topical treatment of mild to moderate acne vulgaris, characterised by comedones, papules and pustules.

CONTRAINDICATIONS

Isotrex Gel should not be used in patients with known hypersensitivity to any of the ingredients.

Isotrex Gel should not be used in patients with a personal or family history of skin cancer.

PRECAUTIONS

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

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

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

Sensitivity to sunlight

Albino mice treated with isotretinoin and exposed to ultraviolet light (artificial light) demonstrated an accelerated appearance of sunlight induced skin tumours; mice treated with isotretinoin but not exposed to ultraviolet light did not develop tumours. The significance of these findings as related to human beings is unknown.

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.

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

Effects on 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.

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 and appreciable depression of spermatogenesis were noted after approximately 30 weeks at isotretinoin dose levels of 20 or 60 mg/kg/day given orally. However, in studies of men receiving oral isotretinoin, no significant effects have been seen on semen parameters.

Use in pregnancy

Pregnancy Category D

Reproduction studies conducted in rabbits using isotretinoin gel applied topically at a dose of 0.5 mg/kg/day have revealed no harm to the fetus. This dose is approximately 19 times greater than the human dose of isotretinoin, based on body surface area and assuming use of 1 g gel by a 50 kg patient. However, isotretinoin has been shown to be teratogenic in multiple animal species (mice, rats, hamsters, rabbits and monkeys) following oral administration, and humans are recognised to be more sensitive to the teratogenic effects of isotretinoin than laboratory animal species. Teratogenicity has also been demonstrated with tretinoin an isomer and metabolite of isotretinoin, following topical administration in rats.

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.

Use during lactation

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.

Paediatric use

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

There are no specific recommendations for use in the elderly.

Renal impairment

No dosage adjustment is necessary.

Renal impairment is not expected to result in systemic exposure to isotretinoin of clinical significance. This is because negligible percutaneous absorption of isotretinoin follows topical application (*see Pharmacokinetics*).

Hepatic impairment

No dosage adjustment is necessary.

Hepatic impairment is not expected to result in systemic exposure to isotretinoin of clinical significance. This is because negligible percutaneous absorption of isotretinoin follows topical application (*see Pharmacokinetics*).

Genotoxicity

Isotretinoin was negative in assays for mutagenicity in bacteria (Ames test), chromosomal aberrations *in vitro* (Chinese hamster lung cells) and *in vivo* (mouse micronucleus test), and unscheduled DNA synthesis *in vitro* (rat hepatocytes).

Carcinogenicity

In Fischer 344 rats given oral isotretinoin up to 32 mg/kg/day for 18 months or longer, there was an increased incidence of pheochromocytomas 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 pheochromocytoma in Fischer 344 rats, the relevance of this finding to humans is uncertain.

The tumourigenic potential of UV irradiation was increased with concurrent dermal exposure to isotretinoin at dose levels ≥ 100 mg/kg in hairless albino mice. Although the relevance of this finding to humans is not clear, patients should minimise exposure to sunlight or artificial UV sources (see also Sensitivity to sunlight).

INTERACTIONS WITH OTHER MEDICINES

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).

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: $\geq 1/10$
Common: $\geq 1/100$ to $< 1/10$
Uncommon: $\geq 1/1000$ to $< 1/100$
Rare: $\geq 1/10000$ 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

DOSAGE AND ADMINISTRATION

Adults and adolescents

Apply Isotrex Gel sparingly over the whole affected area once daily, at night (see *Precautions*).

Patients should be advised that 6-8 weeks of treatment may be required before a therapeutic effect is observed. The safety and effectiveness of Isotrex Gel have not been investigated in clinical studies for treatment periods longer than 14 weeks.

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.

OVERDOSAGE

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 overdosage (e.g. hypervitaminosis A) is highly unlikely.

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

Treatment

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Topical gel containing isotretinoin 0.05 % w/w (0.05 g per 100 g gel). Presented in aluminium tube, fitted with screw cap.

Pack size is 30 g.

Store below 25°C.

Keep container tightly closed when not in use. Contents are flammable. Keep away from fire, flame or heat. Do not leave Isotrex Gel in direct sunlight.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4
436 Johnston Street
Abbotsford Victoria 3067

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):

30 November 1993

Date of most recent amendment: 28 October 2013

Version 7.0

