PRODUCT MONOGRAPH

KETODERM

(Ketoconazole, USP)

2% Cream

Topical Antifungal Agent

TaroPharma
A Division of Taro Pharmaceuticals Inc.
130 East Drive
Brampton, Ontario
L6T 1C1

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ACTION

In vitro studies suggest that the antifungal properties of Ketoconazole may be related to its ability to impair the synthesis of ergosterol, a component of fungal and yeast cell membranes. Without the availability of this essential sterol, there are morphological alterations of the fungal and yeast cell membranes manifested as abnormal membranous inclusions between the cell wall and the plasma membrane. The inhibition of ergosterol synthesis has been attributed to interference with the reactions involved in the removal of the 14-" -methyl group of the precursor of ergosterol, lanosterol (1).

INDICATIONS

KETODERM (ketoconazole) cream 2% may be indicated for the topical treatment of tinea pedis, tinea corporis and tinea cruris caused by Trichophyton rubrum, T. mentagrophytes and Epidermophyton floccosum; and in the treatment of tinea versicolor (pityriasis) caused by Malassezia furfur (Pityrosporum orbiculare); and in the treatment of seborrhoeic dermatitis caused by Pityrosporum ovale; and in the treatment of cutaneous candidiasis caused by Candida albicans.

CONTRAINDICATIONS

KETODERM (ketoconazole) cream 2% is contraindicated in persons who have shown hypersensitivity to the active or excipient ingredients of this formulation.

WARNINGS

KETODERM (ketoconazole) cream 2% should never be employed for the treatment of infections of the eye.

To prevent a rebound effect after stopping a prolonged treatment with topical corticosteroids, it is recommended to continue applying a mild topical corticosteroid in the morning and to apply KETODERM cream in the evening, and to subsequently and gradually withdraw the steroid therapy over a period of 2-3 weeks.

PRECAUTIONS

If a reaction suggesting sensitivity or chemical irritation should occur, use of KETODERM (ketoconazole) cream 2% should be promptly discontinued.

Limited short term studies in animals and in human volunteers on whom limited quantities of KETODERM cream 2% were tested have failed to demonstrate absorption of ketoconazole in detectable amounts. Due to the teratogenic nature of the active ingredient, ketoconazole, caution should be exercised when KETODERM cream 2% is administered to pregnant or nursing women.

Cross sensitivity with miconazole and other imidazoles may exist and caution is suggested

when KETODERM cream 2% is employed in patients with known sensitivity to imidazoles.

ADVERSE REACTIONS

Short-term studies indicate that Ketoconazole Cream 2% is well tolerated by the skin. During clinical trials, 43 (5.0%) of 867 patients treated with the cream and 3 (1.8%) of 167 patients treated with placebo reported side effects consisting mainly of severe irritation, pruritus and stinging. One of the patients treated with Ketoconazole Cream 2% developed a painful allergic reaction (swelling of the foot).

In rare circumstances, allergic local skin phenomena such as contact dermatitis have been associated with ketoconazole cream 2% or one of its components, namely sodium sulfite or propylene glycol.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There has been no experience with overdosage of Ketoconazole Cream 2%. Treatment should include general supportive measures.

DOSAGE AND ADMINISTRATION

When clinically warranted, therapy with KETODERM (ketoconazole) cream 2% may be initiated while results of culture and susceptibility tests are pending. Treatment should be adjusted according to the findings.

KETODERM cream 2% should be applied to the affected and immediate surrounding area

in patients with the following conditions:

CONDITIONS	FREQUENCY	DURATION
Tinea pedis	once daily	4-6 weeks
Tinea corporis	once daily	3-4 weeks
Tinea cruris	once daily	2-4 weeks
Tinea versicolor	once daily	2-3 weeks
Cutaneous candidiasis	once daily	2-3 weeks

More resistant cases may be treated twice daily depending on patient response.

Seborrheic dermatitis	twice daily	4 weeks

The full course of therapy should be followed to reduce the possibility of recurrence. If however, there is no response within the recommended treatment period, the diagnosis should be re-evaluated.

The safety of Ketoconazole cream 2% has not been established with treatment periods exceeding those recommended, therefore, treatment must not exceed the recommended duration of therapy indicated above.

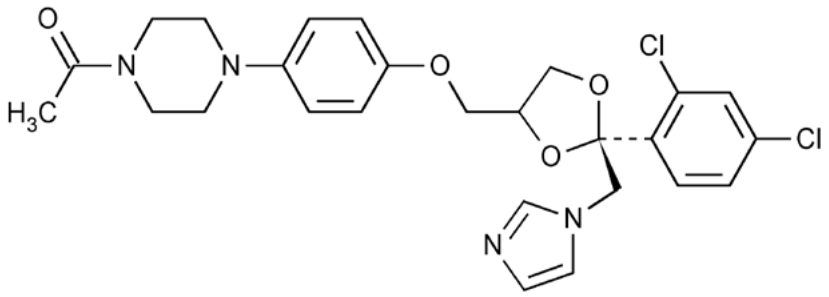
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: ketoconazole

Chemical Name: cis-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2 -(1H- imidazol -1 - ylmethyl) - 1,3-dioxolan-4-yl] methoxy] phenyl] piperazine

Structural Formula:



Molecular formula: $C_{26}H_{28}Cl_2N_4O_4$

Molecular weight: 531.44

Description: Ketoconazole is an almost white to slightly beige coloured powder which is freely soluble in chloroform, methanol and diluted hydrochloric acid; sparingly soluble in 2-propanol and acetone and practically insoluble in water.

Composition:

KETODERM cream 2% contains the broad-spectrum synthetic antifungal agent, ketoconazole, formulated in an aqueous cream vehicle consisting of propylene glycol,

stearyl and cetyl alcohols, sorbitan monostearate, polysorbate 60, isopropyl myristate, butylated hydroxyanisole (BHA), polysorbate 80 and water.

Stability and Storage Recommendations:

Store at room temperature, between 15° and 25°C. Keep from freezing.

AVAILABILITY OF DOSAGE FORM

KETODERM cream 2% is a white odourless cream containing 20 mg ketoconazole per gram and is supplied in 30 g tubes.

MYCOLOGY

In Vitro

In yeast and fungal cells, ergosterol is the main sterol regulating membrane permeability. Ketoconazole inhibits the biosynthesis of ergosterol and affects the synthesis of triglycerides and phospholipids.

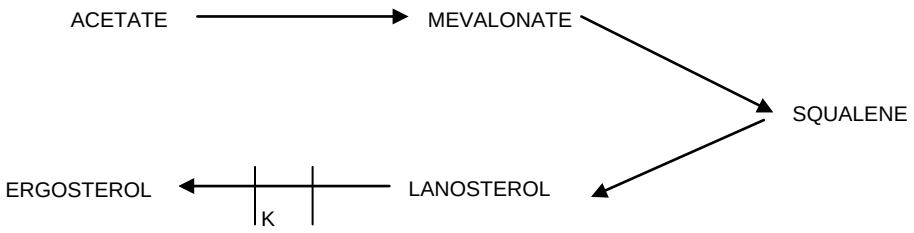


Diagram 1: Site of action of ketoconazole (K) on the steroid biosynthetic pathway in the fungal cell.

Morphologically, ketoconazole-induced alterations are characterized by the presence of abnormal membranous inclusions between the cell wall and plasma membrane. Changes

in oxidative and peroxidative enzyme activities, leading to an intracellular build up of toxic concentrations of hydrogen peroxide, may contribute to the observed deterioration of subcellular organelles and to cell necrosis.

In vitro studies have shown that ketoconazole is fungistatic at low concentrations (0.01 - 0.1 μg/mL) and fungicidal at very high concentrations (1 - 10 μg/mL) against dermatophytes.

Table 1

MIC of Ketoconazole against Dermatophytes and Yeasts (2)

Organism	No. of strains tested	Range of minimal inhibitory concentrations (μg/mL)
Dermatophytes		
Microsporum canis	24	0.1 - 64
Microsporum audouini	4	2 - 64
Microsporum gypseum	9	0.1 - 64
Microsporum cookei	1	1
Trichophyton mentagrophytes	24	0.1 - 20
Trichophyton rubrum	75	10^{-5} - 128
Trichophyton ajelloi	1	1
Trichophyton schoenleini	1	1
Trichophyton tonsurans	35	0.25 - 16
Epidermophyton floccosum	23	0.1 - 8
Yeasts		
Candida albicans	472	0.02 - 80
Candida tropicalis	45	0.1 - 64

Candida pseudotropicalis	2	25 - 50
Candida guilliermondii	4	0.4 - 50
Candida krusei	14	0.2 - 3.1
Candida parapsilosis	18	0.2 - 64
Candida stellatoidea	1	0.8
Cryptococcus neoformans	39	0.1 - 32
Torulopsis glabrata	124	0.8 - 64
Rhodotorula mucilanginosa	1	0.1
Trichosporon cutaneum	1	0.1

In vivo studies have shown ketoconazole topical cream to be effective against dermatophyte infections of the skin in guinea pigs. Applied at concentrations > 1.0% in a PEG base once a day for 14 days, ketoconazole cream healed or improved experimental infections due to Trichophyton mentagrophytes and Microsporum canis.

PHARMACOLOGY

The systemic absorption of Ketoconazole cream 2% was not measurable in Beagle dogs. When applied to both intact and abraded skin at a daily dose of 80 mg for 28 days, the cream produced plasma levels of ketoconazole which did not exceed the detection limit of the HPLC- method (0.002 μg/mL).

The systemic absorption of Ketoconazole cream 2% was not detectable in man. A single application of 10 g cream to the back, arms and chest did not produce quantifiable blood levels.

TOXICOLOGY

Animal Studies

Subacute Dermal Toxicity in New Zealand White Rabbits and Albino Guinea Pigs

Ketoconazole cream 2% at doses of 0, 0.5, 1.0 and 2.0 g/kg was devoid of any irritating effect in 16 male and 16 female New Zealand white rabbits (4 per group). Daily applications to the intact or abraded skin up to 2 g/kg for 30 days produced a barely perceptible irritation that was no different from that with 2 g/kg of the vehicle; a single application of 0.1 mg to the conjunctiva of 6 male New Zealand white rabbits was not irritating.

Ketoconazole cream 2% was also devoid of any allergenic or sensitizing potential in 10 male and 10 female albino guinea pigs. Induction comprised 10 topical applications of 0.5 mg Ketoconazole cream 2% using occlusive patches and 2 intradermal injections of Freund's complete adjuvant over a 4 week period. Subsequently, animals were challenged with a single 48-hour application of the same dose. This dose was applied to a region which had not been previously treated. Neither the patches used for the induction experiment nor those used in the challenge reaction elicited oedema or erythema.

Carcinogenicity

When ketoconazole was admixed in the diet, such that daily oral doses up to 80 mg/kg/day were provided to Swiss Albino mice for a period of 18 months and also to Wistar rats for a period of 24 months, there was no evidence of oncogenic activity.

Mutagenicity

The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation at any stage of germ cell development. The Ames Salmonella microsomal activator assay was also negative.

Reproduction and Teratology

Ketoconazole has been shown to be embryotoxic and teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day. When ketoconazole was given to rats by gavage, evidence of maternal toxicity and embryotoxicity was seen with doses as low as 10 mg/kg.

Human Studies

Dermal Irritancy

In 10 female volunteers treated topically with 5 $\mu g/cm^2$ Ketoconazole cream 2%, exposure to longwave ultraviolet or visible light did not produce any wheel and flare reaction.

Twenty-five volunteers received a series of 6 applications (2 per week) of 10 $\mu g/cm^2$ of Ketoconazole cream 2% on an occlusive dressing applied to the back skin for 24 hours. Following removal of the patch, the skin was exposed to three minimal erythema doses from a Xenon Solar Simulator. Ten days after the last exposure the subjects were challenged with 5 $\mu g/cm^2$ Ketoconazole cream 2% applied to an untreated site of the skin for 24 hours and subsequently exposed to long ultraviolet light. Ketoconazole cream 2% was shown to be devoid of any detectable photocontact allergenic potential.

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