PRODUCT MONOGRAPH

NIZORAL®

(ketoconazole 2% shampoo)

Therapeutic Classification

Topical Antifungal Agent

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NAME OF DRUG

NIZORAL® shampoo (ketoconazole 2% shampoo)

THERAPEUTIC CLASSIFICATION

Topical antifungal agent

ACTIONS

In vitro studies suggest that the antifungal properties of NIZORAL® (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-α-methyl group of the precursor of ergosterol, lanosterol.

Except for its specific pharmacologic effect, i.e., a sporicidal or fungicidal activity, ketoconazole when formulated in a 2% shampoo is not expected to exert any other pharmacodynamic effect when applied topically on the skin or hair.

INDICATIONS

NIZORAL® (ketoconazole) 2% shampoo is indicated for the topical treatment and prophylaxis of conditions in which the yeast Pityrosporum is involved, such as pityriasis capitis (dandruff). NIZORAL® shampoo is also indicated for seborrheic dermatitis.

CONTRAINDICATIONS

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

WARNINGS

Irritation may occur when NIZORAL® (ketoconazole) 2% shampoo is used immediately after prolonged treatment with topical corticosteroids. To prevent a rebound effect after stopping a prolonged treatment with topical corticosteroids, it is recommended to continue applying a mild topical corticosteroid at the onset of treatment with NIZORAL® shampoo, 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 NIZORAL® (ketoconazole) 2% shampoo should be discontinued.

There are no adequate and well-controlled studies in pregnant or lactating women. NIZORAL® shampoo does not produce detectable blood levels after topical application to the scalp. Plasma levels were detected after topical administration of NIZORAL® shampoo on the whole body. There are no known risks associated with the use of NIZORAL® shampoo 2% in pregnancy or lactation. There were reports of spontaneous abortion and anencephaly after exposure to NIZORAL® shampoo during pregnancy, although there is insufficient information to confirm any association between NIZORAL® shampoo and these abnormal pregnancy outcomes. However, due to the teratogenic nature of the active ingredient, ketoconazole, the use of NIZORAL® shampoo is not recommended in pregnant or nursing women except under the advice of a physician.

Clinical data on the use of NIZORAL® shampoo in children under 12 are not available; therefore, such use is not recommended except under the advice of a physician.

ADVERSE REACTIONS

Clinical Trial Data

The safety of NIZORAL® Shampoo 2% was evaluated in 2890 subjects in 22 clinical trials where NIZORAL® Shampoo 2% was administered topically to the scalp and/or skin.

No adverse drug reactions (ADRs) were reported in ≥1% of NIZORAL® Shampoo 2% -treated subjects.

Adverse drug reactions that occurred in <1% of NIZORAL® Shampoo 2%-treated subjects in the clinical datasets are listed in Table 1.

Table 1. Adverse Drug Reactions Reported in <1% of 2890 NIZORAL® Shampoo 2%-treated Subjects in 22 Clinical Trials
System Organ Class
Preferred Term
Eye Disorders
Eye irritation
Increased lacrimation
General Disorders and Administration Site Conditions
Application site erythema
Application site irritation
Application site hypersensitivity
Application site pruritus
Application site pustules
Application site reaction
Immune System Disorders
Hypersensitivity
Infections and Infestations
Folliculitis
Nervous System Disorders
Dysgeusia
Skin and Subcutaneous Tissue Disorders
Acne
Alopecia
Dermatitis contact
Dry skin
Hair texture abnormal
Rash
Skin burning sensation
Skin disorder
Skin exfoliation

Post-marketing Experience

Adverse drug reactions first identified during post-marketing experience with NIZORAL® Shampoo 2% are included in Table 2. In this table, the frequencies are provided according to the following convention:

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
Very rare	<1/10,000, including isolated reports

In Table 2, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 2. Adverse Drug Reactions Identified During Post-marketing Experience with NIZORAL® Shampoo 2% by Frequency Category Estimated from Spontaneous Reporting Rates	
Skin and Subcutaneous Tissue Disorders	
Very Rare	Angioedema, Urticaria, Hair colour changes

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Oral ingestion is usually followed by nausea and vomiting due to the detergent. In the event of accidental ingestion, supportive and symptomatic measures should be carried out. In order to avoid aspiration, neither emesis nor gastric lavage should be performed. It has been reported that ketoconazole cannot be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

Adults and children over 12 years of age: NIZORAL® (ketoconazole) 2% shampoo (5 to 10 mL) should be applied to the wet scalp, worked into a lather and left on for 3-5 minutes before rinsing with water. As with other shampoos, care should be taken to keep the shampoo out of the eyes and off the eyelids.

Treatment:

Twice weekly for 2 to 4 weeks.

Prophylaxis:

Once every one or two weeks.

PHARMACEUTICAL INFORMATION

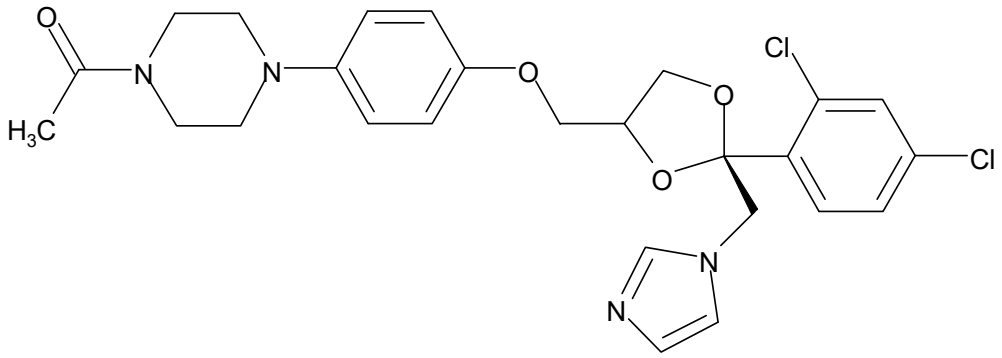
CHEMISTRY

Trade Name: NIZORAL®

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: NIZORAL® (ketoconazole) 2% shampoo is a viscous pink - orange liquid with an herbal bouquet. NIZORAL® 2% shampoo contains the broad-spectrum synthetic antifungal agent, ketoconazole, formulated in a shampoo

vehicle consisting of sodium laureth sulphate, disodium monolaureth sulphosuccinate, coconut fatty acid diethanolamide, laurdimonium hydrolyzed animal collagen, macrogol 120 methyl glucose dioleate, perfume bouquet, imidurea, hydrochloric acid, sodium hydroxide, sodium choloride, erythrosin and water.

DOSAGE FORM

Availability:

NIZORAL® (ketoconazole) 2% shampoo contains 20 mg ketoconazole per gram. It is supplied in HDPE flasks containing 60 mL or 120 mL shampoo.

Storage:

NIZORAL® 2% shampoo should be stored at 15-30°C.

MYCOLOGY

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.

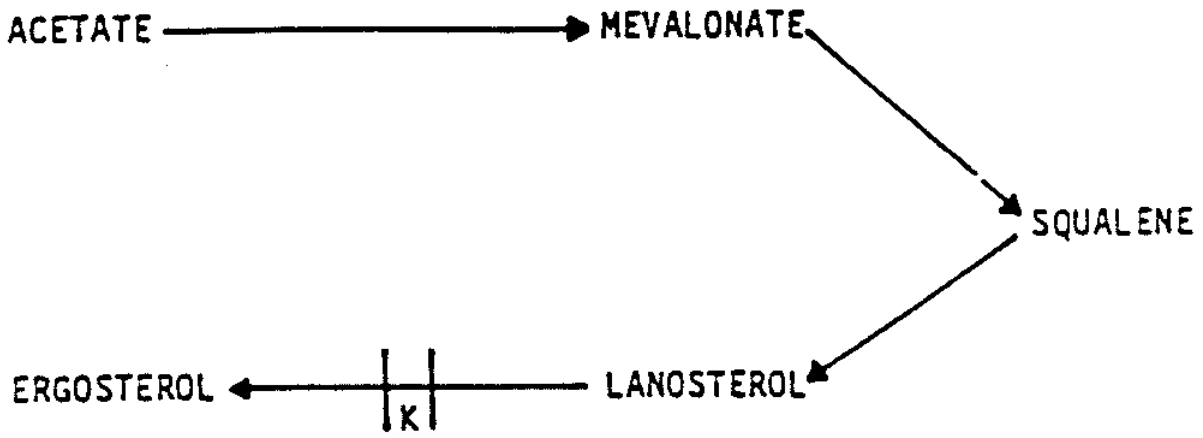


Diagram 1: Site of action of ketoconazole (K) on the steroid biosynthetic pathway in the fungal cell.

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.

The minimum inhibitory concentration of ketoconazole against a variety of yeasts and fungi can be observed in the following table.

Table 3: MIC's of ketoconazole against dermatophytes and yeasts

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	0.2 - 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
Pityrosporum ovale	1	0.1

From: "Ketoconazole in the Management of Fungal Disease", Edited by H.B. Levine, Ph.D., ADIS Press, Pages 57-67

Ketoconazole is a potent antifungal agent with a pronounced fungicidal activity against both the yeast and the mycelial form of Pityrosporum ovale. Pityrosporum ovale was inhibited at a ketoconazole concentration of 0.1 μg/mL.

The development of resistance to oral ketoconazole over a one year treatment period has been reported in 2 patients treated for mucocutaneous candidiasis, however, in vitro sensitivities pre and post treatment were determined by different techniques.

PHARMACOLOGY

Dermal absorption of ketoconazole was studied in a 28-day dermal irritation study in rabbits. After 28 days of daily application of the shampoo at dose levels of 0, 2, 20 or 50 mg ketoconazole/kg on intact and abraded skin, plasma concentrations of ketoconazole were below the detection limit (5 ng/mL) of the HPLC assay. This indicates a lack of any measurable percutaneous absorption of ketoconazole from the shampoo formulation, even after repeated daily application and after prolonged dermal contact.

In humans, plasma concentrations of ketconazole were not detectable after topical administration of NIZORAL® Shampoo 2% on the scalp. Plasma levels were detected after topical administration of NIZORAL® Shampoo 2% on the whole body.

TOXICOLOGY

Topical toxicity studies with ketoconazole 2% shampoo:

The topical toxicity of ketoconazole 2% shampoo was evaluated in rabbits in a primary dermal irritation study, in two primary eye irritation studies, in two subchronic dermal irritation studies and in a chronic dermal toxicity study.

The results are summarized in Table 4.

Table 4: Topical irritation studies with ketoconazole 2% shampoo in rabbits

TYPE OF IRRITATION STUDY	SITE OF APPLICATION	DURATION OF OBSERVATION (DAYS)	DOSAGE OF 2% SHAMPOO	DURATION OF TREATMENT
Primary dermal	Dermal (occlusive)	7	0.3 mL	Single dose
Primary eye	Ocular	14	0.1 mL	Single dose
Primary eye	Ocular	7	0.1 mL of 15% dilution	Single dose
Subchronic dermal	Dermal (semi-open)	28	0.1, 1, 2.5 mL/kg*	28 days
Subchronic dermal (10% degraded shampoo)	Dermal (semi-open)	28	2.5 mL/kg**	28 days
Chronic dermal	Dermal (semi-open)	6 months	0.1, 1,* 2.5 mL/kg	6 months

* Corresponding to 2, 20 and 50 mg ketoconazole per kg body weight.
** Corresponding to 50 mg ketoconazole/kg body weight (non-degraded shampoo) and to 45 mg ketoconazole/kg body weight with 5 mg degradation products/kg body weight (10% degraded shampoo).

Primary dermal irritation study:

The primary dermal irritation was evaluated in rabbits for 7 days by the standard patch technique. Ketoconazole 2% shampoo, applied for 6 hours under an occlusive patch, elicited a primary dermal irritation index of 6.7 classifying it as a severe irritant. The occlusive dermal patch irritation test is an exaggerated test situation and the results with ketoconazole are similar to those for other undiluted shampoos.

Primary ocular irritation study:

The primary eye irritation was studied following the instillation of both undiluted and diluted ketoconazole 2% shampoo into the conjunctival sac of rabbits. The undiluted formulation was classified as positive for irritation. A 15% dilution of the ketoconazole 2% shampoo was classified as negative, as only slight erythema and chemosis were observed.

The data obtained with the diluted form is considered more relevant to the human situation because a small amount (5 to 10 mL) of ketoconazole 2% shampoo is normally spread over the wet scalp and is consequently diluted.

Subchronic dermal irritation study:

Ketoconazole 2% shampoo was applied to the clipped skin, (either abraded or intact), on the backs of rabbits. This was done daily for 28 days. The shampoo was held in place under a semi-open patch for a one hour exposure period. The residual shampoo was then washed from the skin with warm water and the area was dried with soft cloths. The volumes administered were 0.1, 1 and 2.5 mL of shampoo/kg body weight, corresponding to 2, 20 and 50 mg of ketoconazole/kg body weight.

The parameters studied were: mortality, clinical signs, body weight, food consumption, plasma ketoconazole levels, haematology, serum chemistry, organ weights, gross pathology and histopathology of the normal and treated skin.

No treatment-related adverse effects or lesions were observed. Ketoconazole was not detectable in the plasma.

Subchronic dermal irritation study (10% degraded shampoo):

Ketoconazole 2% shampoo (non-degraded or 10% degraded) was applied to the clipped skin (either abraded or intact) on the backs of rabbits. Rabbits were exposed 5 days/week during 28 days. The shampoo was held in place under a semi-open patch for a one hour exposure period. The residual shampoo was then washed from the skin with warm water and the area was dried with soft cloths. The volume administered was 2.5 mL of shampoo/kg body weight, corresponding to 50 mg of ketoconazole/kg body weight (non-degraded shampoo) or 45 mg of ketoconazole/kg body weight and 5 mg degradation products/kg body weight (degraded shampoo).

The parameters studied were: mortality, clinical observations, body weight, haematology, serum analysis, organ weights and gross pathology.

Both treatments were well tolerated and did not result in any dermal or systemic toxic effects.

Chronic dermal toxicity study:

Ketoconazole 2% shampoo was applied to the clipped (abraded or intact) skin on the backs of rabbits. This was done daily for 26 weeks. The shampoo was held in place under a semi-open patch for a one hour exposure period. The residual shampoo was then washed from the skin with warm water and the area was dried with soft cloths. The volumes administered were 0.1, 1 and 2.5 mL of shampoo/kg body weight, corresponding to 2, 20 and 50 mg of ketoconazole/kg body weight. The study also included a placebo group (vehicle not containing ketoconazole).

The parameters studied were: mortality, clinical observations, body weight, haematology, serum analysis, organ weight, gross pathology and histopathology.

The treatments were well tolerated and did not result in dermal or systemic toxic effects. The same lack of adverse effects was observed for the placebo formulation. In addition, the absence of a time-dependent increase of dermal irritation further indicates no sensitization potential.

Carcinogenicity:

Albino Swiss mice and Wistar rats both received doses of 0, 5, 20 and 80 mg/kg per day of ketoconazole administered via the diet for 18 months and 24 months respectively. There were no statistically significant differences between groups in the incidence or type of tumours.

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 in any stage of germ cell development. The Ames Salmonella microsomal activator assay was also negative.

Reproduction and Teratology:

Ketoconazole has been shown to be teratogenic (syndactyly, oligodactyly, abnormal head and leg formation) when given in the diet at 80 mg/kg per 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.

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