PRODUCT MONOGRAPH

OXIZOLE®
(Oxiconazole Nitrate)

1% Cream

Topical Antifungal Agent

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Control # 089170

PRODUCT MONOGRAPH

OXIZOLE®

(oxiconazole nitrate)

Cream 1%

Potency declared as oxiconazole

THERAPEUTIC CLASSIFICATION

TOPICAL ANTIFUNGAL AGENT

ACTION AND CLINICAL PHARMACOLOGY

Oxiconazole nitrate is a broad-spectrum imidazole derivative whose antifungal activity is derived primarily from the inhibition of ergosterol biosynthesis, which is critical for cellular membrane integrity. It has fungicidal or fungistatic activity in vitro against a number of pathogenic fungi including the following dermatophytes, and yeasts: *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Trichophyton violaceum*, *Epidermophyton floccosum*, *Microsporum canis*, *Microsporum audouini*, *Microsporum gypseum*, *Candida albicans*, and *Malassezia furfur*.

Five hours after application of 2.5 mg/cm^2 of oxiconazole nitrate cream onto human skin, the concentration of oxiconazole nitrate was demonstrated to be 16.2 μmol in the epidermis, 3.64 μmol in the upper corium, and 1.29 μmol in the deeper corium. Systemic absorption of oxiconazole nitrate appears to be low. Less than 0.3% of the applied dose was recovered in the urine of volunteer subjects up to five days after application. Feces were not analyzed for the drug, and it is not known whether the absorption is higher than that estimated by recovery of drug in urine.

INDICATIONS AND CLINICAL USE

OXIZOLE (oxiconazole nitrate) Cream is indicated for the topical treatment of athlete's foot (tinea pedis) due to *Trichophyton rubrum*, *Trichophyton mentagrophytes* or *Epidermophyton floccosum*.

CONTRAINDICATIONS

OXIZOLE (oxiconazole nitrate) Cream is contraindicated in individuals who have shown hypersensitivity to oxiconazole and/or any of its components.

WARNINGS

OXIZOLE (oxiconazole nitrate) Cream is for external use only - not for ophthalmic or intravaginal use.

PRECAUTIONS

General: If skin sensitization occurs, discontinue topical administration and institute appropriate therapy as required.

Use in Pregnancy:

Reproduction studies have been performed in rabbits, rats and mice at oral doses up to 100, 150 and 200 mg/kg per day, respectively, and revealed no evidence of harm to the foetus due to oxiconazole nitrate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, OXIZOLE preparation should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Nursing Mothers:

Since oxiconazole is excreted in human milk, caution should be exercised when the drug is administered to a nursing woman. Although human data relating concentrations of oxiconazole in milk were not obtained, after subcutaneous administration of 5 mg/kg to female rats, the milk: plasma ratio at 1.5 - 12 hours was in the range of 3.0 - 8.0.

ADVERSE REACTIONS

During clinical trials, 37 (4.2%) of 879 patients treated with oxiconazole nitrate 1% cream reported drug related adverse reactions, including pruritus 1.6%, burning (1.4%), irritation (0.5%), erythema, stinging and allergic contact dermatitis (0.2% each) and folliculitis, fissuring, maceration rash and nodules (0.1% each).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Acute overdosage of oxiconazole nitrate in humans has not been reported to date.

Symptoms:

Animal studies have shown oxiconazole nitrate to be a central nervous system depressant and tissue irritant when administered orally or by injection.

Treatment:

In cases of accidental ingestion, gastric lavage should be considered, otherwise, the treatment should be symptomatic.

DOSAGE AND ADMINISTRATION

In patients with tinea pedis, OXIZOLE (oxiconazole nitrate) Cream should be applied to cover affected and surrounding areas twice daily (in the morning and evening). Medication should be gently massaged into the skin. Tinea pedis should be treated for one month to reduce the possibility of recurrence. If a patient shows no clinical improvement after the treatment period, the diagnosis should be reviewed.

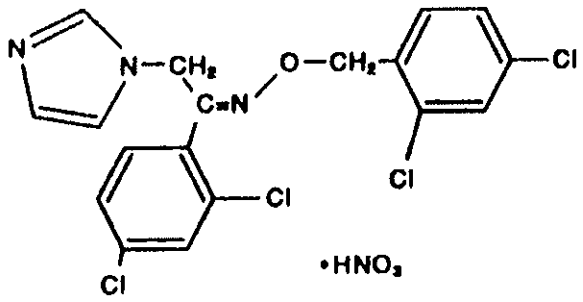
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Oxiconazole nitrate

Chemical Name: 2',4'-dichloro-2-imidazole-1-ylacetophenone (Z[O-2,4-dichlorobenzyl)oxime] mono-nitrate

Structural Formula



Molecular Formula: $C_{18}H_{13}ON_3Cl_4.HNO_3$

Molecular Weight: 492.16

Description

Oxiconazole nitrate is a practically odourless, nearly white fine powder. Soluble in methanol; sparingly soluble in ethanol, chloroform, and acetone; and very sparingly soluble in water.

pka ≈ 6.2

Melting point is 137-143°C with decomposition.

Composition

OXIZOLE Cream contains 10 mg/g of oxiconazole (as oxiconazole nitrate) in a white to off-white, opaque cream base of purified water, white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, cetyl alcohol, and benzoic acid 0.2% as a preservative.

Storage:

Store OXIZOLE Cream at 15°C-30°C.

AVAILABILITY OF DOSAGE FORMS

OXIZOLE Cream 1%	2 g (physician's samples), 15 g, 30 g and 60 g tubes containing 10 mg/g of oxiconazole (as oxiconazole nitrate) in a white to off-white opaque cream base.

INFORMATION FOR THE CONSUMER

OXIZOLE CREAM

OXIZOLE (oxiconazole nitrate):

OXIZOLE cream is a medication indicated for the treatment of athlete's foot (tinea pedis). The active ingredient of OXIZOLE is oxiconazole nitrate which is a broad spectrum antifungal agent.

.Instructions for use

1. Before applying OXIZOLE cream, the affected areas should be cleansed with a mild soap and water and gently dried.

2. Apply OXIZOLE cream to cover affected and surrounding areas twice daily in the morning and the evening. Gently massage medication into the skin. If used for the treatment of athlete's foot, pay special attention to spaces between the toes and wear well-fitted, ventilated shoes and cotton socks.

3. The hands should be washed after application.

4. For the treatment of athlete's foot, OXIZOLE cream should be used for one month.

5. Use OXIZOLE cream for the full treatment period even though symptoms may have subsided. This will assure healing and decrease the possibility of recurrence.

6. When treating athlete's foot, if no effects or improvement of your condition is seen after four weeks consult your physician to have the diagnosis reviewed.

Precautions

1. OXIZOLE cream should be used up to a maximum of four consecutive weeks of treatment.

2. If irritation or sensitivity develop with the use of OXIZOLE cream, treatment should be discontinued and your physician should be consulted.

3. Notify your physician if the area of application reveals signs of increased irritation (redness, itching, burning, swelling or oozing).

4. Avoid the use of bandages or wrappings over the area of the body on which OXIZOLE cream is applied unless otherwise directed by your physician.

5. OXIZOLE cream should be kept away from the eyes, nose, mouth and other mucous membranes. If contact with the eyes occurs, rinse thoroughly with water.

6. Do not use OXIZOLE Cream for infection of the scalp or nails.

Use in pregnancy: OXIZOLE preparation should not be used during pregnancy except on the advice of a doctor.

Use in nursing mothers: OXIZOLE preparation should not be used by a nursing mother except on the advice of a doctor.

Pediatric use: OXIZOLE preparation should not be used on children under the age of 12 except on the advice of a doctor.

Note: Store OXIZOLE Cream at 15°C - 30°C.

WARNING:

OXIZOLE cream is for external use only - not for ophthalmic or intravaginal use.

MICROBIOLOGY

The fungicidal activity of oxiconazole results primarily from the inhibition of ergosterol synthesis, which is needed for cytoplasmic membrane integrity. It has in vitro activity against a wide range of organisms.

In vitro, oxiconazole is active against many strains of clinical isolates of the following dermatophytic organisms: *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum*.

Oxiconazole has also been shown to be active against the following microorganisms in vitro; however, clinical efficacy has not been established: *Trichophyton tonsurans*, *Trichophyton violaceum*, *Microsporum canis*, *Microsporum audouini*, *Microsporum gypseum*, *Candida albicans*, and *Malassezia furfur*.

Oxiconazole demonstrated a broad spectrum of activity. There was a wide range of activity against yeast (0.001 mg/L to 100 mg/L) while the highest overall activity was seen against *Cryptococcus neoformans* (mean MIC=0.025 mg/L). The dematiaceous fungi appeared to be the most susceptible organisms to oxiconazole nitrate (range of MIC 0.001-0.01 mg/L) while most species of molds and dermatophytes had low MIC values, especially medically important strains of *Trichophyton mentagrophytes* (MIC=0.8 mg/L) and *Trichophyton rubrum* (MIC=0.16 mg/L).

PHARMACOLOGY

Animal Pharmacology

Studies in animals demonstrated that oxiconazole has minimal pharmacologic effects, even at high doses. In mice, oral doses of 1,000 mg/kg decreased motility and motor coordination; mild symptoms of central nervous system depression were also noted. No effects were observed on the cardiovascular and respiratory systems. A mild anti-diuretic effect was seen at high doses (250 mg/kg orally; 100 mg/kg ip). There was significant dose-related prolongation of the hexobarbital sleeping time in the mouse after oral administration of oxiconazole.

Human Pharmacology

Two clinical trials conducted in patients with acute symptomatic tinea pedis, have demonstrated that 78% of the subjects treated with OXIZOLE Cream either once or twice daily showed a mycological cure compared to 33% with patients treated with a placebo cream. A mycological cure was declared only when both the KOH reading and the culture were negative. Two weeks after the end of the treatment, 43% and 52% of the patients treated with OXIZOLE Cream once or twice daily, respectively, were clinically cured as opposed to only 14% of the vehicle treated patients (p values ≤ 0.038). A clinical cure was declared upon the finding of a mycological cure in conjunction with a global response of cleared or excellent.

IN-VITRO SUSCEPTIBILITY OF 121 CLINICAL ISOLATES OF MICROORGANISMS TO OXICONAZOLE

Microorganisms	Number of Isolates	CUMULATIVE % OF ISOLATES INHIBITED AT MIC (MG/L)							
		≤0.063	0.125	0.25	0.5	1	2	4	≥8
Epidermophyton floccosum	10	100							
Microsporum audouini	16				12.5	93.7	100		
Microsporum Canis	15			26.7	46.7	100			
Microsporum gypsum	10		20	20	30	60	100		
Trichophyton mentagrophytes	15		40	46.7	86.7	86.7	100		
Trichophyton rubrum	15	20	46.7	60	93.3	100			
Trichophyton tonsurans	15		80	100					
Exophiala werneckii	7	42.8	71.4	85.7	100				
Malassezia Furfur	18	66.7			72.2		77.8	83.3	100

Fungistatic concentrations of oxiconazole

on Casitone solid medium

Microorganism from culture collection	No. of Strains	Mean of MIC mg/L	(Range of MIC) mg/L
Yeasts[b]			
Candida albicans	65	11.12	(0.1-100)
Candida tropicalis	12	100	
Candida krusei	10	0.5	(0.03-1)
Candida guilliermondii	8	0.8	(0.3-1)
Candida parapsilosis	16	1	(0.03-10)
Torulopsis glabrata	15	3	(0.3-30)
Cryptococcus neoformans	33	0.025	(0.001-0.3)
Molds[b]			
Aspergillus fumigatus	21	7.0	(3-10)
Aspergillus niger	9	0.66	(0.1-10)
Aspergillus nidulans	5	1.0	(0.3-3)
Dermatophytes[a]			
Epidermophyton floccosum	--	0.063	--
Trichophyton mentagrophytes	21	0.8	(0.1-3)
Trichophyton rubrum	9	0.16	(0.03-1)
Dematiaceous fungi			
Fonsecaea spp	5	0.03	(0.001-0.01)
Cladosporium spp	4	0.003	(0.001-0.01)

[a]MIC: Minimal inhibitory concentration read after 2-3 days of incubation at 37°C.
[b]MIC: Minimal inhibitory concentration read after 7 days of incubation at 30°C

REPRODUCTION AND TERATOGENICITY

Oxiconazole nitrate was not embryotoxic or teratogenic at doses up to 15 mg/kg/day in mice or rats or up to 100 mg/kg/day in rabbits. Higher doses in rats and mice produced a prolonged gestation period and labour during parturition, decreased perinatal viability and some intrauterine deaths. However, no drug related morphological abnormalities were observed and treatments lasting from pairing through gestation and lactation did not affect fertility or general reproductive performance of the F0 and F1 generations. The development of F1 and F2 generations was not affected by treatment.

MUTAGENICITY

A comprehensive range of genotoxicity studies has been conducted with oxiconazole nitrate. These consisted of tests for microbial mutation, *in vitro* mammalian mutation, *in vitro* cytogenetics and *in vivo* cytogenics. The tests consistently demonstrated the lack of genotoxic potential of oxiconazole nitrate.

TOXICOLOGY

Acute Toxicity

LD_{50} VALUES FOR OXICONAZOLE NITRATE

Species (Strain)	Group Size	Route	LD_{50} (mg/kg)	Symptoms
NMRI mice	10M/10F	IV	46-47.5	Ataxia, prone-or side position, tremors, clonic or tonic spasms.
Wistar rat	10M/10F	IV	45.5-56	Ataxia, prone-or side position, tremors, clonic or tonic spasms.
NMRI mice	10M	IP	460	Ataxia, prone-or side position, clonic spasms hypersalivation and dyspnoea.
Wistar rat	10M/10F	IP	680	Sedation, prone-or side position, ptosis, pilo-erection, hypersalivation and dyspnoea.
NMRI mice	10M	Gavage	3850	Sedation, pilo-erection, ptosis, ataxia, clonic-tonic spasms and hypersalivation.

CHRONIC TOXICITY

Species (Strain)	Group Size	Route of Administration	Dose mg/kg/da (unless specified)	Duration	Formulation	Results
Mouse NMRI	10M	IP	100 200 300 400	5 da	Suspension	LD_{50} = 240 mg/kg/da
Mouse NMRI	10M	Oral	1000 2000 3000 500EN 750EN 1000EN	5 da	Suspension	LD_{50} approx. 1500 mg/kg/da for oxicon. nitrate; 920 mg/ kg/da for econazole nitrate (control).
Rabbit NZ White	10M+10F	Dermal	0 250 500 1000	26 wk	1% Cream	NOEL = 250 mg cream/kg/day. Local dose-related skin irritation at 500 & 1000 mg/kd/day dose levels; effect was reversible. Mild acanthosis & minimal hyperkeratosis; effect was reversible after 4 weeks.

CHRONIC TOXICITY

Species (Strain)	Group Size	Route of Administration	Dose mg/kg/da (unless specified)	Duration	Formulation	Results
Dog	2M+4F	IV IV IV †SC IV †SC IV †SC	0 1 5 5 15 15 15EN 15EN	4 wk 4 wk 2 wk 2 wk 1 wk 1 wk 1 wk 1 wk	1% Solution	NOEL = 1 mg/kg/da. Liver cell dissociation at 5 & 15 mg/kg/da. Severe local damage from SC injections.
Dog	1M+1F	Dermal	0 2 g/da per shoulder	28 da	1% Ointment	No localized effects on skin.
Dog	2M+4F	Oral	0 5 25 150	13 wk	Capsule	NOEL = 25 mg/kg/da; 150 mg/kg/da increase in ALP, SGPT & SGOT, decrease in cholesterol, BWT decreased; diarrhea; fatty liver

CHRONIC TOXICITY

Species (Strain)	Group Size	Route of Administration	Dose mg/kg/da (unless specified)	Duration	Formulation	Results
Rat Wistar	5M+5F	IP	50 100 200 300 400 500	5 da	Suspension	LD50 = 265 mg/kg/da
Rat Wistar	20M+20F	Dermal	0 10 20 50 (1g/kg of 0%,1%, 2%,5% Cream to 10% surface area)	35 da	1% Cream 2% Cream 5% Cream	NOEL = 1% cream. 2% & 5% cream caused skin irritation & hyperkeratosis; 15% mortality with 5% cream. No effect on estrus cycle. Full recovery after 35 day.
Rat Wistar SLD SPF	20M+20F	SC	0 0.2 1 5 25	26 wk	Suspension	NOEL = 1 mg/kg/da. Effects on uterus & estrus cycles. Feed & eater consumption & BWT decrease. Female BWT increase. Various other effects due to formulation only.
Rat Fuellins-dorf	12M+12F	IP	0 5 10 25 25EN	6 wk	1% Solution	NOEL = 10mg/kg/da. Decrease in body wt. gain in males at 25 mg/kg/da. Study complication-peritonitis caused by IP inj. of solvent.
Rat Fuellins-dorf	18M+18F	Diet	0 5 35 250	13 wk	Feed	NOEL = 35 mg/kg/da. Body wt. decreased at 250 mg/kg/da in males only; liver wt. Increased in M&F without histological or biochemical change.

SPECIAL HUMAN STUDIES

Phototoxicity

The phototoxic potential of 1% oxiconazole cream and the cream vehicle alone were assessed in ten healthy adult volunteers, two females and eight males.

The creams were applied in aliquots of 0.1 mL to duplicate randomly selected, skin sites of the mid-back of each subject and covered with occlusive patches. After six hours, patches on one side of the back were removed and the test sites immediately exposed to 20 J/cm^2 of long wave ultra violet light (UVA) and high energy visible light. The sites on the opposite side acted as controls and were not irradiated. Reactions were graded immediately and 24 and 48 hours after irradiation.

There were no instances of phototoxicity or unexpected reactions to either of the creams. It may be concluded that neither 1% oxiconazole cream nor the cream vehicle alone possess detectable phototoxic potential in humans.

Photoallergenicity

The test was carried out using 1% oxiconazole cream and the cream vehicle alone. The test creams were applied to randomly selected 2 x 2 sq cm skin in place for 24 hours. Each patch was then removed and the site immediately exposed to three MEDs from the simulator. This sequence was repeated 48 hours later and subsequently thereafter to the same sites for a total of six exposures at the rate of two exposures per week.

Ten days after the last induction exposure, the subjects were challenged by applying 0.1 gram of 1% oxiconazole cream and of the cream vehicle alone to new, duplicate, randomly selected normal skin sites on the back. The sites were occluded for 24 hours and the patches were then removed from one side and the sites exposed to 4 J/cm^2 of UVA irradiation and high energy visible light from the simulator. The unirradiated, treated, sites acted as controls as did an irradiated, untreated, site. All sites were evaluated at 48 and 72 hours after patch removal and irradiation.

Twenty-seven of the thirty subjects completed the study. Three subjects withdrew for reasons unrelated to the test. No reactions of any kind were observed in any of the twenty-seven subjects completing the study. Upon challenge, no reactions to either of the creams were seen.

It may be concluded that 1% oxiconazole cream and the cream vehicle alone do not possess detectable photoallergenic potential in humans.

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