OXICONAZOLE NITRATE- oxiconazole nitrate cream
Taro Pharmaceuticals U.S.A., Inc.

Oxiconazole Nitrate
Cream, 1%[1]

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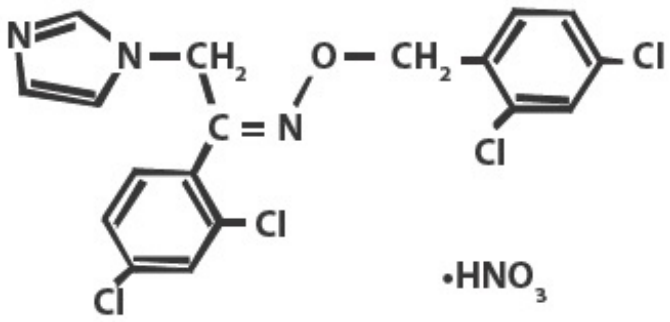
[1] **Potency expressed as oxiconazole**

Rx Only
FOR TOPICAL DERMATOLOGIC USE ONLY—
NOT FOR OPHTHALMIC OR INTRAVAGINAL USE

DESCRIPTION

Oxiconazole nitrate cream, 1% contains the antifungal active compound oxiconazole nitrate. This formulation is for topical dermatologic use only.

Chemically, oxiconazole nitrate is 2',4'-dichloro-2-imidazol-1-ylacetophenone *(Z)*-[*0*-(2,4-dichlorobenzyl)oxime], mononitrate. The compound has the molecular formula $C_{18}H_{13}ON_3CI_4 \cdot HNO_3$, a molecular weight of 492.15, and the following structural formula:



Oxiconazole nitrate is a nearly white crystalline powder, soluble in methanol; sparingly soluble in ethanol, chloroform, and acetone; and very slightly soluble in water.

Oxiconazole nitrate cream, 1% contains 10 mg of oxiconazole per gram of cream in a white to off-white cream base of cetyl alcohol, polysorbate 60, propylene glycol, purified water, stearyl alcohol, white petrolatum, and benzoic acid 0.2% as a preservative.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The penetration of oxiconazole nitrate into different layers of the skin was assessed using an in vitro permeation technique with human skin. 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 is low. Using radiolabeled drug, less than 0.3% of the applied dose of oxiconazole nitrate was recovered in the urine of volunteer subjects up to 5 days after application of the cream formulation. Neither in vitro nor in vivo studies have been conducted to establish relative activity between the lotion and cream formulations.

Microbiology

Oxiconazole nitrate is an imidazole derivative whose antifungal activity is derived primarily from the inhibition of ergosterol biosynthesis, which is critical for cellular membrane integrity. It has in vitro activity against a wide range of pathogenic fungi.

Oxiconazole has been shown to be active against most strains of the following organisms both in vitro and in clinical infections at indicated body sites (see INDICATIONS AND USAGE):

Epidermophyton floccosum
Trichophyton mentagrophytes
Trichophyton rubrum
Malassezia furfur

The following in vitro data are available; **however, their clinical significance is unknown.** Oxiconazole exhibits satisfactory in vitro minimum inhibitory concentrations (MICs) against most strains of the following organisms; however, the safety and efficacy of oxiconazole in treating clinical infections due to these organisms have not been established in adequate and well-controlled clinical trials:

Candida albicans
Microsporum audouini
Microsporum canis
Microsporum gypseum
Trichophyton tonsurans
Trichophyton violaceum

INDICATIONS AND USAGE

Oxiconazole nitrate cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*. Oxiconazole nitrate cream is indicated for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES).

Oxiconazole nitrate cream may be used in pediatric patients for tinea corporis, tinea cruris, tinea pedis, and tinea (pityriasis) versicolor; however, these indications for which oxiconazole nitrate cream has been shown to be effective rarely occur in children below the age of 12.

CONTRAINDICATIONS

Oxiconazole nitrate cream is contraindicated in individuals who have shown hypersensitivity to any of their components.

WARNINGS

Oxiconazole nitrate cream is not for ophthalmic or intravaginal use.

PRECAUTIONS

General

Oxiconazole nitrate cream is for external dermal use only. Avoid introduction of oxiconazole nitrate cream into the eyes or vagina. If a reaction suggesting sensitivity or chemical irritation should occur with the use of oxiconazole nitrate cream, treatment should be discontinued and appropriate therapy

instituted. If signs of epidermal irritation should occur, the drug should be discontinued.

Information for Patients

The patient should be instructed to:

1. Use oxiconazole nitrate cream as directed by the physician. The hands should be washed after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth, and other mucous membranes. Oxiconazole nitrate cream is for external use only.
2. Use the medication for the **full** treatment time recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after 2 to 4 weeks, or sooner if the condition worsens (see below).
3. Inform the physician if the area of application shows signs of increased irritation, itching, burning, blistering, swelling, or oozing.
4. Avoid the use of occlusive dressings unless otherwise directed by the physician.
5. Do not use this medication for any disorder other than that for which it was prescribed.

Drug Interactions

Potential drug interactions between oxiconazole nitrate cream and other drugs have not been systematically evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no evidence of mutagenic effect was found in 2 mutation assays (Ames test and Chinese hamster V79 in vitro cell mutation assay) or in 2 cytogenetic assays (human peripheral blood lymphocyte in vitro chromosome aberration assay and in vivo micronucleus assay in mice).

Reproductive studies revealed no impairment of fertility in rats at oral doses of 3 mg/kg/day in females (1 time the human dose based on mg/m^2) and 15 mg/kg/day in males (4 times the human dose based on mg/m^2). However, at doses above this level, the following effects were observed: a reduction in the fertility parameters of males and females, a reduction in the number of sperm in vaginal smears, extended estrous cycle, and a decrease in mating frequency.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rabbits, rats, and mice at oral doses up to 100, 150, and 200 mg/kg/day (57, 40, and 27 times the human dose based on mg/m^2), respectively, and revealed no evidence of harm to the fetus 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, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Because oxiconazole is excreted in human milk, caution should be exercised when the drug is administered to a nursing woman.

Pediatric Use

Oxiconazole nitrate cream may be used in pediatric patients for tinea corporis, tinea cruris, tinea pedis, and tinea (pityriasis) versicolor; however, these indications for which oxiconazole nitrate cream has been shown to be effective rarely occur in children below the age of 12.

Geriatric Use

A limited number of patients at or above 60 years of age (n ~ 396) have been treated with oxiconazole nitrate cream in US and non-US clinical trials, and a limited number (n = 43) have been treated with oxiconazole nitrate lotion in US clinical trials. The number of patients is too small to permit separate analysis of efficacy and safety. No adverse events were reported with oxiconazole nitrate lotion in geriatric patients, and the adverse reactions reported with oxiconazole nitrate cream in this population were similar to those reported by younger patients. Based on available data, no adjustment of dosage of oxiconazole nitrate cream in geriatric patients is warranted.

ADVERSE REACTIONS

During clinical trials, of 955 patients treated with oxiconazole nitrate cream, 1%, 41 (4.3%) reported adverse reactions thought to be related to drug therapy. These reactions included pruritus (1.6%); burning (1.4%); irritation and allergic contact dermatitis (0.4% each); folliculitis (0.3%); erythema (0.2%); and papules, fissure, maceration, rash, stinging, and nodules (0.1% each).

In a controlled, multicenter clinical trial of 269 patients treated with oxiconazole nitrate lotion, 1%, 7 (2.6%) reported adverse reactions thought to be related to drug therapy. These reactions included burning and stinging (0.7% each) and pruritus, scaling, tingling, pain, and dyshidrotic eczema (0.4% each).

OVERDOSAGE

When 5% oxiconazole cream (5 times the concentration of the marketed product) was applied at a rate of 1 g/kg to approximately 10% of body surface area of a group of 40 male and female rats for 35 days, 3 deaths and severe dermal inflammation were reported. No overdoses in humans have been reported with use of oxiconazole nitrate cream or lotion.

DOSAGE AND ADMINISTRATION

Oxiconazole nitrate cream should be applied to affected and immediately surrounding areas once to twice daily in patients with tinea pedis, tinea corporis, or tinea cruris. Oxiconazole nitrate cream should be applied once daily in the treatment of tinea (pityriasis) versicolor. Tinea corporis, tinea cruris, and tinea (pityriasis) versicolor should be treated for 2 weeks and tinea pedis for 1 month to reduce the possibility of recurrence. If a patient shows no clinical improvement after the treatment period, the diagnosis should be reviewed.

Note: Tinea (pityriasis) versicolor may give rise to hyperpigmented or hypopigmented patches on the trunk that may extend to the neck, arms, and upper thighs. Treatment of the infection may not immediately result in restoration of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and incidental sun exposure. Although tinea (pityriasis) versicolor is not contagious, it may recur because the organism that causes the disease is part of the normal skin flora.

CLINICAL STUDIES

The following definitions were applied to the clinical and microbiological outcomes in patients enrolled in the clinical trials that form the basis for the approvals of Oxiconazole nitrate lotion and Oxiconazole nitrate cream.

Definitions

1. Mycological Cure: No evidence (culture and KOH preparation) of the baseline (original) pathogen in a specimen from the affected area taken at the 2-week post-treatment visit (for tinea [pityriasis] versicolor, mycological cure was limited to KOH only).
2. Treatment Success: Both a global evaluation of ≥90% clinical improvement and a microbiologic

eradication (see above) at the 2-week post-treatment visit.

Tinea Pedis

THERE ARE NO HEAD-TO-HEAD COMPARISON TRIALS OF THE OXICONAZOLE NITRATE CREAM AND LOTION FORMULATIONS IN THE TREATMENT OF TINEA PEDIS.

Lotion Formulation

The clinical trial for the lotion formulation line extension involved 332 evaluable patients with clinically and microbiologically established tinea pedis. Of these evaluable patients, 64% were diagnosed with hyperkeratotic plantar tinea pedis and 28% with interdigital tinea pedis. Seventy-seven percent (77%) had disease secondary to infection with *Trichophyton rubrum*, 18% had disease secondary to infection with *Trichophyton mentagrophytes*, and 4% had disease secondary to infection with *Epidermophyton floccosum*.

The results of this clinical trial at the 2-week post-treatment follow-up visit are shown in the following table:

Patient Outcome	**Oxiconazole nitrate lotion**		**Vehicle**
	b.i.d	**q.d.**	
Myocological cure	67%	64%	28%
Treatment success	41%	34%	10%

In this study, the improvement and cure rates of the b.i.d.- and q.d.-treated groups did not differ significantly (95% confidence interval) from each other but were statistically (95% confidence interval) superior to the vehicle-treated group.

Cream Formulation

The two pivotal trials for the cream formulation involved 281 evaluable patients (total from both trials) with clinically and microbiologically established tinea pedis.

The combined results of these two clinical trials at the 2-week post-treatment follow-up visit are shown in the following table:

Patient Outcome	**Oxiconazole nitrate cream**		**Vehicle**
	b.i.d	**q.d.**	
Myocological cure	77%	79%	33%
Treatment success	52%	43%	14%

All the improvement and cure rates of the b.i.d.- and q.d.- treated groups did not differ significantly (95% confidence interval) from each other but were statistically (95% confidence interval) superior to the vehicle-treated group.

In addition, pediatric data (95 children ages 10 and under) available with the cream formulation indicate that it is safe and effective for use in children when used as directed. Adverse events were reported in 2 children; 1 child was reported to have reddening of the skin and 1 child was reported to have eczema-like skin alterations.

Tinea (pityriasis) Versicolor

Two pivotal clinical trials of oxiconazole nitrate cream in tinea (pityriasis) versicolor involved 219 evaluable patients in the q day oxiconazole nitrate and vehicle arms of the trial with clinical and mycological evidence of tinea (pityriasis) versicolor. Patients were treated for 2 weeks with oxiconazole nitrate cream once daily, or with cream vehicle. The combined results of these clinical

trials at the 2-week post-treatment follow-up visit are shown in the following table. These results are based on 207 patients (110 in the oxiconazole nitrate group and 97 in the vehicle group) with efficacy evaluations at this visit.

Patient Outcome	Oxiconazole nitrate cream	Vehicle
	q.d.	
Myocological cure	88%	67%
Treatment success	83%	62%

Only once a day was shown in both studies to be statistically superior to vehicle for all efficacy parameters at 2 weeks and follow-up.

HOW SUPPLIED

Oxiconazole Nitrate Cream, 1% is supplied in:

15 g tubes - (NDC 51672-1359-1)
30 g tubes - (NDC 51672-1359-2)
60 g tubes - (NDC 51672-1359-3)
90 g tubes - (NDC 51672-1359-8)

Store at 20° – 25°C (68° – 77°F) [See USP Controlled Room Temperature].

Mfd. by: Taro Pharmaceuticals Inc.
Brampton, Ontario, Canada L6T 1C1
Dist. by: **Taro Pharmaceuticals U.S.A., Inc.**
Hawthorne, NY 10532
Issued: July, 2015
PK-7064-0 101

PRINCIPAL DISPLAY PANEL - 15 g Tube Carton

NDC 51672-1359-1

15 g

Oxiconazole Nitrate
Cream , 1%*
*Potency expressed as oxiconazole.

For Topical Dermatological Use Only.
Not for Ophthalmic or Intravaginal Use.

Rx only

Keep this and all medications out of the reach of children.

TARO

OXICONAZOLE NITRATE

oxiconazole nitrate cream

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51672-1359
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Oxiconazole Nitrate (UNII: RQ8UL4C17S) (Oxiconazole - UNII:C668Q9I33J)	Oxiconazole	10 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
cetyl alcohol (UNII: 936JST6JCN)	
polysorbate 60 (UNII: CAL22UVI4M)	
propylene glycol (UNII: 6DC9Q167V3)	
water (UNII: 059QF0KO0R)	
stearyl alcohol (UNII: 2KR89I4H1Y)	
petrolatum (UNII: 4T6H12BN9U)	
benzoic acid (UNII: 8SKN0B0MIM)	

Product Characteristics			
Color	WHITE (white to off-white)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51672-1359-1	1 in 1 CARTON	03/07/2016	
1		15 g in 1 TUBE; Type 0: Not a Combination Product		
2	NDC:51672-1359-2	1 in 1 CARTON	03/07/2016	
2		30 g in 1 TUBE; Type 0: Not a Combination Product		
3	NDC:51672-1359-3	1 in 1 CARTON	03/07/2016	
3		60 g in 1 TUBE; Type 0: Not a Combination Product		
4	NDC:51672-1359-8	1 in 1 CARTON	03/07/2016	
4		90 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205076	03/07/2016	

Labeler - Taro Pharmaceuticals U.S.A., Inc. (145186370)

Establishment

Name	Address	ID/FEI	Business Operations
Taro Pharmaceuticals Inc.		206263295	MANUFACTURE(51672-1359) , API MANUFACTURE(51672-1359)

Revised: 12/2019 Taro Pharmaceuticals U.S.A., Inc.