Oxiconazole Nitrate Cream, 1%

*Potency expressed as oxiconazole*

**DESCRIPTION**
Oxiconazole nitrate cream, 1% contains the anti-fungal active ingredient oxiconazole nitrate. This formulation is for topical dermatologic use only.

**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/cm² of oxiconazole nitrate cream onto human skin, the concentration of oxiconazole nitrate was determined 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 anti-fungal 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.

**Metabolism:** Oxiconazole nitrate is a molecular weight of 492.15, and the following structural formula:

![Structural formula](image)

The compound has the molecular formula C$_{14}$H$_{15}$N$_{2}$O$_{3}$N$_{2}$-(2,4-dichlorobenzyl)oxime, mononitrate. Oxiconazole nitrate cream is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris, 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 its 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 areas.
2. Avoid contact with the eyes, nose, mouth, and other mucous membranes. Oxiconazole nitrate cream is for external use only.
3. Use the medication for the full treatment recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after 2-4 weeks, or sooner if the condition worsens (see below).
4. Inform the physician if the area of application shows signs of increased irritation, itching, burning, biting, swelling, or oozing.
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 mammalian assays (Salmonella typhimurium and Chinese hamster V79 in vitro cell mutagenesis assay) or in 2 cytokinesis assays (human peripheral blood lymphocytes in vitro chromosome aberration assay and in vivo micronucleus assay in mice).

Reproductive studies revealed no impairment of fertility in rats or oral doses of 3 mg/kg/day in females (1 time the human dose based on mg/m²) and 15 mg/kg/day in males (4 times the human dose based on mg/m²). However, at doses above this level, the following effects were observed: 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/m²), 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 in the US have been treated with oxiconazole nitrate cream.
Nitrate cream in US and non-US clinical trials, and a limited number (n = 43) have been treated with oxiconazole nitrate cream 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 cream 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 951 patients treated with oxiconazole nitrate cream, 1%, 41% (13%) 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 cream, 1%, 7 (0.6%) 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.

DOSE 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. Treatment success of oxiconazole nitrate cream in tinea (pityriasis) versicolor involved 281 evaluable patients (total from both formulations) of the baseline (original) pathogen in a study extending 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 approval of Oxiconazole nitrate ointment and Oxiconazole nitrate cream.

Definition:

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 microbiological eradication at the 2-week post-treatment visit.

Tinea Pedis: There is no head-to-head comparison trial 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 352 evaluable patients with clinically and microbiologically established tinea pedis. Of these evaluable patients, 64% were diagnosed with hyperkeratotic plantar tinea pedis and 26% with interdigital tinea pedis. Seventy-seven percent (77%) had disease secondary to infection with Trichophyton rubrum; 19% had disease secondary to infection with Trichophyton mentagrophytes and 4% had disease secondary to infection with Epidermophyton floccosum.

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

<table>
<thead>
<tr>
<th>Patient Outcome</th>
<th>Oxiconazole nitrate cream</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycological cure</td>
<td>Treatment success</td>
<td>67%</td>
</tr>
<tr>
<td>Treatment success</td>
<td>64%</td>
<td>34%</td>
</tr>
</tbody>
</table>

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

Creme Formulation: The two pivotal trials for the cream formulation involved 261 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:

<table>
<thead>
<tr>
<th>Patient Outcome</th>
<th>Oxiconazole nitrate cream</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycological cure</td>
<td>Treatment success</td>
<td>77%</td>
</tr>
<tr>
<td>Treatment success</td>
<td>79%</td>
<td>43%</td>
</tr>
</tbody>
</table>

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 intervals) 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 (pityriasis) versicolor involved 218 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 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.

<table>
<thead>
<tr>
<th>Patient Outcome</th>
<th>Oxiconazole nitrate cream</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycological cure</td>
<td>Treatment success</td>
<td>85%</td>
</tr>
<tr>
<td>Treatment success</td>
<td>85%</td>
<td>67%</td>
</tr>
</tbody>
</table>

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), and 90 g tubes - NDC 51672-1359-4).

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

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