NAFTIN® (naftifine hydrochloride) gel, for topical use

Initial U.S. Approval: 1988

INDICATIONS AND USAGE

NAFTIN® Gel is an allylamine antifungal indicated for the treatment of interdigital tinea pedis caused by the organisms Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum. (1)

DOSAGE AND ADMINISTRATION

Apply a thin layer of NAFTIN® Gel once daily to the affected areas plus an approximate ½ inch margin of healthy surrounding skin for 2 weeks. (2)

For topical use only. NAFTIN® Gel is not for ophthalmic, oral, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Gel, 2%, (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

If redness or irritation develops with the use of NAFTIN® Gel treatment should be discontinued. (5.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sebela Pharmaceuticals Inc. at 1-888-271-4621 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NAFTIN® Gel is indicated for the treatment of interdigital tinea pedis caused by the organisms Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum. (1)

2 DOSAGE AND ADMINISTRATION

Apply a thin layer of NAFTIN® Gel once daily to the affected areas plus an approximate ½ inch margin of healthy surrounding skin for 2 weeks. For topical use only. NAFTIN® Gel is not for ophthalmic, oral, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS

Gel, 2%. Each gram contains 20 mg of naftifine hydrochloride in a vehicle. The trial subjects were 12 to 92 years old, were primarily male (76%), and were 59% Caucasian, 38% Black or African American, and 23% Hispanic or Latino. Subjects received doses once daily, topically, for 2 weeks to cover the affected skin areas plus a ½-inch margin of surrounding healthy skin. The most common adverse reactions were application site reactions which occurred at the rate of 2% in NAFTIN® Gel arm versus 1% in vehicle arm. Most adverse reactions were mild in severity.

In an open-label pediatric pharmacokinetics and safety trial 22 pediatric subjects 12-17 years of age with interdigital tinea pedis received NAFTIN® Gel. The incidence of adverse reactions in the pediatric population was similar to that observed in adult population.

Cumulative irritancy testing revealed the potential for NAFTIN® Gel to cause irritation. There was no evidence that NAFTIN® Gel causes contact sensitization, phototoxicity, or photoallergenicity in healthy skin.

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the following adverse reactions have been identified during post-approval use of naftifine hydrochloride: blisters, burning sensation, crust, dryness, erythema/redness, inflammation, irritation, maceration, pain, pruritus (itching), rash, and swelling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on NAFTIN® Gel use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse effects on embryofetal development were seen at oral doses administered during the period of organogenesis up to 37 times the maximum recommended human dose (MRHD) of 3 mg/kg/day (7 times the MRHD based on mg/m² comparison). Subcutaneous doses of 10 and 30 mg/kg/day of naftifine hydrochloride were administered during the period of organogenesis up to 4 times the MRHD in pregnant rats or 7 times the MRHD in pregnant rabbits (see Data).

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Systemic embryofetal development studies were conducted in rats and rabbits. For the comparison of animal to human doses, the MRHD is set at 4.2% gel per day (1.33 mg/kg/day for a 60 kg individual). Oral doses of 30, 100, and 300 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis to pregnant female rats. No treatment-related effects on embryofetal toxicity were noted at doses up to 300 mg/kg/day (37 times the MRHD based on mg/m² comparison). Subcutaneous doses of 10 and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis to pregnant female rats. No treatment-related effects on embryofetal toxicity were noted at 30 mg/kg/day (4 times the MRHD based on mg/m² comparison). Subcutaneous doses of 3, 10, and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis to pregnant female rabbits. No treatment-related effects on embryofetal toxicity were noted at 30 mg/kg/day (7 times the MRHD based on mg/m² comparison). A peri- and post-natal development study was conducted in rats. Oral doses of 30, 100, and 300 mg/kg/day naftifine hydrochloride were administered to female rats from gestational day 14 to lactation day 21. Reduced body weight gain of females during gestation and of offspring during lactation was noted at 300 mg/kg/day (37 times the MRHD based on mg/m² comparison). No developmental toxicity was noted at 100 mg/kg/day (12 times the MRHD based on mg/m² comparison).

8.2 Lactation

Risk Summary

There is no information available on the presence of naftifine hydrochloride in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production after topical application of NAFTIN Gel to women who are breastfeeding. It is not known whether naftifine hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when naftifine hydrochloride is administered to a nursing woman.

The lack of clinical data during lactation precludes a clear determination of the risk NAFTIN Gel to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NAFTIN gel and any potential adverse effects on the breastfed infant from NAFTIN gel or from the underlying maternal condition.
were treated with a mean dose of 4.1 grams NAFTIN® Gel applied to
approximately 4 g/day [see Clinical Pharmacology (12.3)].

Safety and effectiveness were similar to those reported by younger subjects.

11 DESCRIPTION
NAFTIN® Gel is a clear to yellow gel for topical use only. Each gram of NAFTIN® Gel contains 20 mg of naftifine hydrochloride, a synthetic allylamine antifungal compound. Chemically, naftifine HCl is (E)-N-Cinnamyl-N-methyl-1-napthalenemethylamine hydrochloride. The molecular formula is C₂₁H₂₁N•HCl with a molecular weight of 323.86.

The structural formula of naftifine hydrochloride is:

\[
\text{NAFTIN® Gel contains the following inactive ingredients: alcohol, benzyl alcohol, edetate disodium, hydroxylethyl cellulose, purified water, propylene glycol, polysorbate 20 and trolamine.}
\]

12 CLINICAL PHARMACOLOGY
12.1 Pharmacokinetics
NAFTIN® Gel is a topical antifungal drug [see Clinical Pharmacology (12.4)].

12.2 Pharmacodynamics
The pharmacodynamics of NAFTIN® Gel have not been established.

12.3 Pharmacokinetics
In vitro and in vivo bioavailability studies have demonstrated that naftifine penetrates the stratum corneum in sufficient concentration to inhibit the growth of dermatophytes.

Pharmacokinetic analysis of plasma samples from 32 subjects with tinea pedis treated with a mean dose of 3.9 grams NAFTIN® Gel applied once daily to both feet for 14 days showed increased exposure over the treatment period, with a geometric mean (CV%) AUC₀-₂⁴ of 105 (118) ng·hr/mL on Day 1 and an AUC₀-₂⁴ of 70 (59) ng·hr/mL on Day 14. The accumulation ratio based on AUC was approximately 6. Maximum concentration (C_max) also increased over the treatment period; geometric mean (CV%) C_max after a single dose was 0.9 (92) ng/mL on Day 1; C_max on Day 14 was 3.7 (64) ng/mL. Median Tmax was 20.0 hours (range: 8, 24 hours) on Day 14. Trough concentrations increased during the trial period and reached steady state after 11 days. In the same pharmacokinetic trial, the fraction of dose excreted in urine during the treatment period was less than or equal to 0.01% of the applied dose.

In a second trial, the pharmacokinetics of NAFTIN® Gel was evaluated in two pediatric subjects 12-17 years of age with tinea pedis. Subjects were treated with a mean dose of 4.1 grams NAFTIN® Gel applied to the affected area once daily for 14 days. The results showed that the systemic exposure increased over the treatment period. Geometric mean (CV%) AUC₀-₂⁴ was 15.9 (212) ng·hr/mL on Day 1 and 60.0 (131) ng·hr/mL on Day 14. Geometric mean (CV%) C_max after a single dose was 1.40 (154) ng/mL on Day 1 and 3.81 (154) ng/mL on Day 14. The fraction of dose excreted in urine during the treatment period was less than or equal to 0.003% of the applied dose.

12.4 Microbiology
Mechanism of Action
Naftifine is an antifungal that belongs to the allylamine class. Although the exact mechanism of action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squaene 2, 3-epoxidase. The inhibition of enzyme activity by this allylamine results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squaene in the cells.

Mechanism of Resistance
To date, a mechanism of resistance to naftifine has not been identified.

Naftifine has been shown to be active against most isolates of the following fungi, both in vitro and in clinical infections, as described in the INDICATIONS AND USAGE section:

<table>
<thead>
<tr>
<th>Trichophyton rubrum</th>
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<tbody>
<tr>
<td>Trichophyton mentagrophytes</td>
</tr>
<tr>
<td>Epidermophyton floccosum</td>
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</tbody>
</table>

Mechanism of Resistance
To date, a mechanism of resistance to naftifine has not been identified.

NAFTIN® Gel has been evaluated for efficacy in two randomized, double-blind, vehicle-controlled, multicenter trials that included 1175 subjects with symptomatic and dermatophyte culture-positive interdigital tinea pedis. Subjects were randomized to receive NAFTIN® Gel or vehicle. Subjects applied naftifine hydrochloride gel 2% or vehicle to the affected area of the foot once daily for 2 weeks. Signs and symptoms of interdigital tinea pedis (presence or absence of erythema, pruritus, and scaling) were assessed and potassium hydroxide (KOH) examination and dermatophyte culture were performed 6 weeks after the first treatment.

The mean age of the study population was 45 years; 77% were male, and 60% were Caucasian, 35% were Black or African American, and 26% were Hispanic or Latin. At baseline, subjects were confirmed to have signs and symptoms of interdigital tinea pedis, positive KOH exam, and confirmed dermatophyte culture. The primary efficacy endpoint was the proportion of subjects with a complete cure at 6 weeks after the start of treatment (4 weeks after the last treatment). Complete cure was defined as both a clinical cure (absence of erythema, pruritus, and scaling) and mycological cure (negative KOH and dermatophyte culture).

The efficacy results at week 6, four weeks following the end of the treatment, are presented in Table 1 below.

| Table 1 Interdigital Tinea Pedis: Number (% of Subjects with Complete Cure, Effective Treatment, and Mycological Cure at Week 6 Following Treatment with NAFTIN® Gel (Full Analysis Set, Missing Values Treated as Missing Treatment) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Endpoint        | NAFTIN® Gel, 2% | Vehicle         | NAFTIN® Gel, 2% | Vehicle         |
| n (%)           | N=382           | N=179           | N=400           | N=213           |
| Complete Cure   | 164 (77%)       | 3 (2%)          | 104 (26%)       | 7 (3%)          |
| Treatment Effectiveness | 207 (54%)   | 11 (6%)         | 203 (51%)       | 15 (7%)         |
| Mycological Cure | 250 (63%)       | 25 (14%)        | 235 (59%)       | 22 (10%)        |

a. Complete cure is a composite endpoint of both mycological cure and clinical cure. Clinical cure is defined as the absence of erythema, pruritus, and scaling (grade of 0).
b. Effective treatment is a negative KOH preparation and negative dermatophyte culture, erythema, scaling, and pruritis grades of 0 or 1 (absent or nearly absent).
c. Mycological cure is defined as negative KOH and dermatophyte culture.

16 HOW SUPPLIED/STORAGE AND HANDLING
How Supplied
NAFTIN® Gel is a colorless to yellow gel supplied in collapsible tubes in the following sizes:

- 45g – NDC 54766-772-45
- 60g – NDC 54766-772-60

Storage
Store NAFTIN® Gel at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION
- Inform patients that NAFTIN® Gel is for topical use only. NAFTIN® Gel is not intended for ophthalmic, oral, or intravaginal use.
- Patients should be directed to contact their physician if irritation develops with the use of NAFTIN® Gel.

Distributed by
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