HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NAFTIN® Gel safely and effectively. See full prescribing information for NAFTIN® (fluconazole) Gel. 2%
NAFTIN® (fluconazole) hydrochloride Gel, 2% for topical use
Initial U.S. Approval: 1988

RECENT MAJOR CHANGES
Indications and Usage (1)

DOSE AND ADMINISTRATION
Apply a thin layer of NAFTIN® Gel once daily to the affected areas plus an approximate 1-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)

DOSE FORMS AND STRENGTHS
Gel, 2% (3)

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
If a suspected adverse reaction develops with the use of NAFTIN® Gel treatment should be discontinued. (5.1)

ADVERSE REACTIONS
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.

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 semisynthetic antifungal compound.

Chemically, naftifine hydrochloride is (S)-N-Cinnamyl-1-naphthaldehyde hydrochloride. The molecular formula is C27H22N•HCl with a molecular weight of 323.88. The structural formula of naftifine hydrochloride is:

NAFTIN® Gel contains the following inactive ingredients: purified water, propylene glycol, polysorbate 20, alcohol, hydroxyethyl cellulose, benzyl alcohol, trehalose, and edetate disodium.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
The pharmacodynamics of NAFTIN® Gel have not been established.

12.2 Pharmacokinetics
In vitro and in vivo biobalance studies have demonstrated that naftifine penetrates the stratum corneum in sufficient concentrations to achieve the desired therapeutic effect. 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 for 14 days showed increased exposure over the treatment period, with a geometric mean (CV) AUC(0-24h) area under plasma concentration versus time curve from time 0 to 24 hours of 105.1 (118) ng•h/mL on Day 1 and an AUC(0-24h) of 20.09 ng•h/mL on Day 14. The accumulation ratio based on AUC was approximately 6. Maximum concentration (Cmax) also increased over the treatment period, geometric mean (CV) Cmax on Day 1 was 0.9 (0.0) ng/mL on Day 1; Cmax on Day 14 was 3.7 (4.6) ng/mL. Median Tmax was 20.0 hours (range: 8.0, 24 hours) after a single application on Day 1 and 8.0 hours (range: 24, 24 hours) on Day 14. Trough plasma 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 22 pediatric subjects: 12-17 years of age with tinea pedis. Subjects were exposed to a mean dose of 4.1 grams NAFTIN® Gel applied once daily for 14 days. The results showed that the systemic exposure increased over the treatment period. Geometric mean (CV) AUC(0-24h) on Day 1 was 121 (26) ng•h/mL and on Day 14 was 153 (25) ng•h/mL. The accumulation ratio based on AUC was about 6. Maximum concentration (Cmax) also increased over the treatment period, geometric mean (CV) Cmax on Day 1 was 3.7 (4.6) ng/mL on Day 1; Cmax on Day 14 was 4.4 (3.4) ng/mL. The fraction of dose excreted in urine during the treatment period was less than or equal to 0.02% of the applied dose.

1.8 Carcinogenicity
Mechanism of Action
Naftifine is an antifungal agent that belongs to the allylamine class. Although the exact mechanism of action against fungus is not known, naftifine hydrochloride interacts with sterol biosynthesis by inhibiting the enzyme squalene 2,3-epoxidase. The inhibition of enzyme activity by this allylamine decreases in amounts of sterols, especially ergosterol, and is responsible for accumulation of squalene in the cells. Treatment with naftifine for one month does not affect the growth, fertility, or reproduction of rats at doses up to 100 mg/kg/day (12.2X MRHD).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies to evaluate the carcinogenic potential of naftifine hydrochloride have not been performed.

Naftifine hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (mouse lymphoma tk assay and Chinese hamster ovary cell chromosome aberration assay) and one in vivo genotoxicity test (mouse bone marrow micronucleus assay).

Oral administration of naftifine hydrochloride to rats, through multiple gestation, mating, parturition, and lactation, demonstrated no effects on growth, fertility, or reproduction, at doses up to 100 mg/kg/day (12.2X MRHD).

14 CLINICAL STUDIES
NAFTIN® Gel has been evaluated for efficacy in two randomized, double-blind, vehicle-controlled, multicenter trials that included both tinea pedis and tinea interdigitalis. Results of these studies are described in the INDICATIONS AND USAGE section.

15 ADVERSE REACTIONS
Pediatric Use
In two randomized, vehicle-controlled trials, 1143 subjects were treated with NAFTIN® Gel versus 571 subjects treated with the vehicle. Subjects were randomized to receive either vehicle or NAFTIN® Gel (4.1 grams) applied once daily for 14 days. Complete cure was defined as negative KOH preparation and dermatophyte culture at the end of the treatment period. Rates of complete cure and global assessment of efficacy for tinea pedis at endpoint are shown in Table 1.

Table 1: Complete Cure and Global Efficacy Results for Tinea Pedis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>NAFTIN® Gel</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Treatment Complete</td>
<td>322 (78%)</td>
<td>177 (43%)</td>
</tr>
<tr>
<td>Global Efficacy</td>
<td>823 (94%)</td>
<td>272 (59%)</td>
</tr>
</tbody>
</table>

In two randomized, vehicle-controlled trials, 1427 subjects were treated with NAFTIN® Gel versus 723 subjects treated with the vehicle. Subjects were randomized to receive either vehicle or NAFTIN® Gel (4.1 grams) applied once daily for 14 days. Complete cure was defined as a negative KOH preparation and dermatophyte culture at the end of the treatment period. As with tinea pedis, the rates of complete cure and global assessment of efficacy are shown in Table 2. In this trial, the rates of complete cure and global assessment of efficacy were similar to those reported by younger patients.

Table 2: Complete Cure and Global Efficacy Results for Tinea Interdigitalis

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<tbody>
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<td>Treatment Complete</td>
<td>242 (64%)</td>
<td>133 (31%)</td>
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<tr>
<td>Global Efficacy</td>
<td>823 (94%)</td>
<td>272 (59%)</td>
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16 HOW SUPPLIED/STORAGE AND HANDLING
NAFTIN® Gel is a colorless to yellow gel supplied in collapsible tubes in the following size:

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.

Inform patients that NAFTIN® Gel is for topical use only. NAFTIN® Gel is not intended for ophthalmic, oral, or intravaginal use.

18 PATIENT COUNSELING INFORMATION

Section or subsections omitted from the full prescribing information are not listed.

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