NAFTIN®- naftifine hydrochloride gel

NAFTIN® NAFTIFINE HCl 1%

Rx ONLY

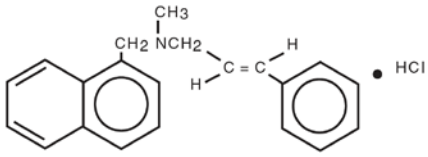
DESCRIPTION

Naftin® Gel, 1% contains the synthetic, broad-spectrum, antifungal agent naftifine hydrochloride. Naftin® Gel, 1% is for topical use only.

CHEMICAL NAME

(E)-N-Cinnamyl-N-methyl-1-naphthalenemethylamine hydrochloride. Naftifine hydrochloride has an empirical formula of $C_{21}H_{21}N$•HCl and a molecular weight of 323.86.

Structural Formula



naftifine hydrochloride

Contains

Active Ingredient

Naftifine hydrochloride 1%.

Inactive Ingredients

Naftin® Gel, 1% contains polysorbate 80, carbomer 934P, diisopropanolamine, edetate disodium, alcohol (52%v/v), and purified water.

CLINICAL PHARMACOLOGY

Naftifine Hydrochloride is a synthetic allylamine derivative. The following *in vitro* data are available, but their clinical significance is unknown. Naftifine hydrochloride has been shown to exhibit fungicidal activity *in vitro* against a broad spectrum of organisms, including *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum, Microsporum canis, Microsporum audouini,* and *Microsporum gypseum,* and fungistatic activity against *Candida* species, including *Candida albicans.* Naftin® Gel, 1% has only been shown to be clinically effective against the disease entities listed in the INDICATIONS AND USAGE section.

Although the exact mechanism of action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2, 3-epoxidase. This inhibition of enzyme activity results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene in the cells.

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.

Following single topical applications of ^{3}H- labeled naftifine gel 1% to the skin of healthy subjects, up to 4.2% of the applied dose was absorbed. Naftifine and/or its metabolites are excreted via the urine and feces with a half-life of approximately two to three days.

INDICATIONS AND USAGE

Naftin® Gel, 1% is indicated for the topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans*[1], *Epidermophyton floccosum*[1].

[1] Efficacy for this organism in this organ system was studied in fewer than 10 infections.

CONTRAINDICATIONS

Naftin® Gel, 1% is contraindicated in individuals who have shown hypersensitivity to any of their components.

WARNINGS

Naftin® Gel, 1% is for topical use only and not for ophthalmic use.

PRECAUTIONS

General

Naftin® Gel, 1%, is for external use only. If irritation or sensitivity develops with the use of Naftin® Gel, 1%, treatment should be discontinued and appropriate therapy instituted.
Diagnosis of the disease should be confirmed either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Information for patients

The patient should be told to:

1. Avoid the use of occlusive dressings or wrappings unless otherwise directed by the physician.
2. Keep Naftin® Gel, 1% away from the eyes, nose, mouth and other mucous membranes.

Carcinogenesis, mutagenesis, impairment of fertility

In a 2-year dermal carcinogenicity study, naftifine hydrochloride cream was administered to Sprague-Dawley rats at topical doses of 1%, 2% and 3% (10, 20, and 30 mg/kg/day naftifine hydrochloride). No drug-related tumors were noted in this study up to the highest dose evaluated in this study of 30 mg/kg/day [3.6 times the maximum recommended human dose (MRHD) based on mg/m^2 comparison].

Naftifine hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames 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, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 100 mg/kg/day (12 times MRHD based on mg/m^2 comparison).

Pregnancy

Teratogenic Effects

Reproduction studies have been performed in rats and rabbits (via oral administration) at doses 150 times or more than the topical human dose and have revealed no evidence of impaired fertility or harm to the fetus due to naftifine. 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

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk,

caution should be exercised when Naftin® Gel, 1 % is administered to a nursing woman.

Pediatric use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

During clinical trials with Naftin® Gel, 1%. the incidence of adverse reactions was as follows: burning/stinging (5.0%), itching (1.0%), erythema (0.5%), rash (0.5%), skin tenderness (0.5%).

DOSAGE AND ADMINISTRATION

A sufficient quantity of Naftin® Gel, 1% should be gently massaged into the affected and surrounding skin areas twice a day, in the morning and evening. The hands should be washed after application. If no clinical improvement is seen after four weeks of treatment with Naftin® Gel, 1%, the patient should be re-evaluated.

HOW SUPPLIED

Naftin® (naftifine hydrochloride) Gel, 1% is supplied in collapsible tubes in the following sizes

40g – NDC 54766-770-40
60g – NDC 54766-770-60
90g – NDC 54766-770-90

Note: Store Naftin® Gel, 1% at room temperature.

Distributed by Sebela Pharmaceuticals Inc.
645 Hembree Parkway, Suite I, Roswell, Georgia 30076
www.sebelapharma.com
Toll Free 1-844-732-3521

Revised 04/2018
PI77040001

NAFTIN®- naftifine hydrochloride cream

NAFTIN® NAFTIFINE HCl 1%

Rx ONLY

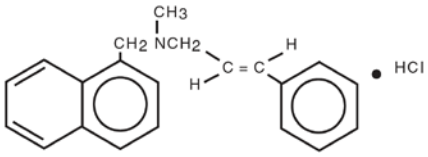
DESCRIPTION

Naftin® Cream, 1% contains the synthetic, broad-spectrum, antifungal agent naftifine hydrochloride. Naftin® Cream 1% is for topical use only.

CHEMICAL NAME

(E)-N-Cinnamyl-N-methyl-1-naphthalenemethylamine hydrochloride. Naftifine hydrochloride has an empirical formula of $C_{21}H_{21}N$•HCl and a molecular weight of 323.86.

Structural Formula



naftifine hydrochloride

Contains

Active Ingredient

Naftifine hydrochloride 1%.

Inactive Ingredients

Naftin® Cream, 1% contains benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol. Hydrochloric acid may be added to adjust pH.

CLINICAL PHARMACOLOGY

Naftifine Hydrochloride is a synthetic allylamine derivative. The following *in vitro* data are available, but their clinical significance is unknown. Naftifine hydrochloride has been shown to exhibit fungicidal activity *in vitro* against a broad spectrum of organisms, including *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum, Microsporum canis, Microsporum audouini,* and *Microsporum gypseum,* and fungistatic activity against *Candida* species, including *Candida albicans.* Naftin® Cream, 1% has only been shown to be clinically effective against the disease entities listed in the INDICATIONS AND USAGE section.

Although the exact mechanism of action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene 2, 3-epoxidase. This inhibition of enzyme activity results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene in the cells.

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.

Following a single topical application of 1% of naftifine cream to the skin of healthy subjects, systemic absorption of naftifine was approximately 6% of the applied dose. Naftifine and/or its metabolites are

excreted via the urine and feces with a half-life of approximately two to three days.

INDICATIONS AND USAGE

Naftin® Cream, 1% is indicated for the topical treatment of tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum, Trichophyton mentagrophytes,* and *Epidermophyton floccosum*.

CONTRAINDICATIONS

Naftin® Cream, 1% is contraindicated in individuals who have shown hypersensitivity to any of their components.

WARNINGS

Naftin® Cream, 1% is for topical use only and not for ophthalmic use.

PRECAUTIONS

General

Naftin® Cream, 1% is for external use only. If irritation or sensitivity develops with the use of Naftin® Cream, 1%, treatment should be discontinued and appropriate therapy instituted.
Diagnosis of the disease should be confirmed either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Information for patients

The patient should be told to:

1. Avoid the use of occlusive dressings or wrappings unless otherwise directed by the physician.
2. Keep Naftin® Cream, 1% away from the eyes, nose, mouth and other mucous membranes.

Carcinogenesis, mutagenesis, impairment of fertility

In a 2-year dermal carcinogenicity study, naftifine hydrochloride cream was administered to Sprague-Dawley rats at topical doses of 1%, 2% and 3% (10, 20, and 30 mg/kg/day naftifine hydrochloride). No drug-related tumors were noted in this study up to the highest dose evaluated in this study of 30 mg/kg/day [3.6 times the maximum recommended human dose (MRHD) based on mg/m^2 comparison].

Naftifine hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames 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, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 100 mg/kg/day (12 times MRHD based on mg/m^2 comparison).

Pregnancy

Teratogenic Effects

Reproduction studies have been performed in rats and rabbits (via oral administration) at doses 150 times or more than the topical human dose and have revealed no evidence of impaired fertility or harm to the fetus due to naftifine. 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

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Naftin® Cream, 1 % is administered to a nursing woman.

Pediatric use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

During clinical trials with Naftin® Cream, 1%, the incidence of adverse reactions was as follows: burning/stinging (6%), dryness (3%), erythema (2%), itching (2%), local irritation (2%).

DOSAGE AND ADMINISTRATION

A sufficient quantity of Naftin® Cream, 1% should be gently massaged into the affected and surrounding skin areas once a day. The hands should be washed after application. If no clinical improvement is seen after four weeks of treatment with Naftin® Cream, 1%, the patient should be re-evaluated.

HOW SUPPLIED

Naftin® (naftifine hydrochloride) Cream, 1% is supplied in collapsible tubes in the following sizes:

60g – NDC 54766-126-60
90g – NDC 54766-126-90

Note: Store Naftin® Cream, 1% below 30°C (86°F).

Distributed by Sebela Pharmaceuticals Inc.
645 Hembree Parkway, Suite I, Roswell, Georgia 30076
www.sebelapharma.com
Toll Free 1-844-732-3521

Revised 04/2018
PI12660001

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NAFTIN® Cream, 2% safely and effectively. See full prescribing information for NAFTIN® (naftifine hydrochloride) Cream, 2%.

NAFTIN® (naftifine hydrochloride) Cream, 2%, for topical use
Initial U.S. Approval: 1988

----------INDICATIONS AND USAGE----------
NAFTIN® Cream is an allylamine antifungal indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum*. (1)

----------DOSAGE AND ADMINISTRATION----------
For topical use only. NAFTIN® Cream is not for ophthalmic, oral, or intravaginal use. (2)

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

----------DOSAGE FORMS AND STRENGTHS----------
Cream: 2% (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
Discontinue treatment if redness or irritation develops with NAFTIN® Cream use. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reaction (≥1%) is pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sebela Pharmaceuticals Inc. at 1-844-732-3521 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NAFTIN® Cream is indicated for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum.*

2 DOSAGE AND ADMINISTRATION

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

3 DOSAGE FORMS AND STRENGTHS

Each gram of NAFTIN® Cream contains 20 mg of naftifine hydrochloride (2%) in a white to off-white base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Adverse Reactions

Discontinue treatment if irritation or sensitivity develops with the use of NAFTIN® Cream. Direct patients to contact their physician if these conditions develop following use of NAFTIN® Cream.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical trials, 903 subjects were exposed to naftifine 1% and 2% cream formulations. A total of 564 subjects with interdigital tinea pedis, tinea cruris, or tinea corporis were treated with NAFTIN® Cream.

In two randomized, vehicle-controlled trials (400 ~~patients~~ subjects were treated with NAFTIN® Cream). The population was 12 to 88 years old, primarily male (79%), 48% Caucasian, 36% Black or African American, 40% Hispanic or Latino and had either predominantly interdigital tinea pedis or tinea cruris. Most subjects received doses once-daily, topically, for 2 weeks to cover the affected skin areas plus a ½ inch margin of surrounding healthy skin. In the two vehicle-controlled trials, 17.5% of NAFTIN® Cream treated subjects experienced an adverse reaction compared with 19.3% of vehicle subjects. The most common adverse reaction (≥1%) is pruritus. Most adverse reactions were mild in severity. The incidence of adverse reactions in the NAFTIN® Cream treated population was not significantly different than in the vehicle treated population.

In a third randomized, vehicle-controlled trial, 116 pediatric subjects with tinea corporis were treated with NAFTIN® Cream. The population was aged ≥2 to <18 years (mean age of 9 years), predominantly male (61%), 47% White, 51% Black or African American, 92% Hispanic or Latino, and infected with tinea corporis. NAFTIN® Cream was topically applied once daily for 2 weeks to all affected body surface areas with tinea corporis plus a ½ inch margin of healthy skin surrounding the affected lesions. The incidence of adverse reactions in the NAFTIN® Cream treated population was not significantly different than in the vehicle treated population.

In two open-label pediatric pharmacokinetics and safety trials, 49 pediatric subjects 2 to <18 years of age with interdigital tinea pedis, tinea cruris, and tinea corporis received NAFTIN® Cream. The incidence of adverse reactions in the pediatric population was similar to that observed in the adult population.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of naftifine hydrochloride: redness/irritation, inflammation, maceration, swelling, burning, blisters, serous drainage, crusting, headache, dizziness, leukopenia, agranulocytosis.
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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with NAFTIN® Cream in pregnant women to inform the drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, no adverse effects on embryofetal development were seen at oral doses administered during the period of organogenesis up to 18 times the maximum recommended human dose (MRHD) in pregnant rats or subcutaneous doses administered during the period of organogenesis up to 2 times the MRHD in pregnant rats or 4 times the MRHD in pregnant rabbits *[see Data]*.

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

Data

Animal Data

Systemic embryofetal development studies were conducted in rats and rabbits. For the comparison of animal to human doses based on body surface area comparison (mg/m^2), the MRHD is set at 8 g 2% cream per day (2.67 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 development were noted at doses up to 300 mg/kg/day (18 times MRHD). 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 development were noted at 30 mg/kg/day (2 times MRHD). 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 development were noted at 30 mg/kg/day (4 times MRHD).

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 the offspring during lactation was noted at 300 mg/kg/day (18 times MRHD). No developmental toxicity was noted at 100 mg/kg/day (6 times MRHD).

8.2 Lactation

Risk Summary

There is no information available on the presence of NAFTIN® Cream in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of NAFTIN® Cream to an infant during lactation; therefore, the development and health benefits of breastfeeding should be considered along with the mother's clinical need for NAFTIN® cream and any potential adverse effects on the breastfed infant from NAFTIN® cream or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of NAFTIN® Cream have been established in pediatric patients age 12 and above with interdigital tinea pedis and tinea cruris and age 2 and above with tinea corporis *[see Clinical Studies (14) and Clinical Pharmacology (12.3)]*.

Use of NAFTIN® Cream in these age groups is supported by evidence from adequate and well controlled studies in adults and children, with additional safety and PK data from two open label trials conducted in 49 pediatric subjects exposed to NAFTIN® Cream *[see Clinical Studies (14) and Clinical Pharmacology (12.3)]*.

Safety and effectiveness of NAFTIN® Cream in the treatment of tinea cruris and interdigital tinea pedis in pediatric patients less than 12 years of age have not been established. Safety and effectiveness of NAFTIN® Cream in the treatment of tinea corporis in pediatric patients less than 2 years of age have not been established.

8.5 Geriatric Use

Clinical studies of NAFTIN® Cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

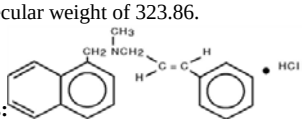
11 DESCRIPTION

NAFTIN® Cream is a white to off-white cream for topical use only. Each gram of (naftifine hydrochloride) Cream contains 20 mg of naftifine hydrochloride (2%), a synthetic allylamine antifungal compound.

Chemically, naftifine HCl is (E)-N-Cinnamyl-N-methyl-1-napthalenemethylamine hydrochloride.

The molecular formula is $C_{21}H_{21}N$•HCl with a molecular weight of 323.86.

The structural formula of naftifine hydrochloride is:



NAFTIN® Cream contains the following inactive ingredients: benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, stearyl alcohol, and hydrochloric acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NAFTIN® Cream is a topical antifungal drug *[see Clinical Pharmacology (12.4)]*

12.2 Pharmacodynamics

The pharmacodynamics of NAFTIN® Cream 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.

The pharmacokinetics of NAFTIN® Cream was evaluated following once-daily topical application for 2 weeks to 21 adult subjects, both males and females, with both tinea pedis and tinea cruris. The median total amount of cream applied was 6.4 g (range 5.3-7.5 g) per day. The results showed that the systemic exposure (i.e., maximum concentration (C_{max}) and area under the curve from time 0 to 24 hours (AUC_{0-24})) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric mean (coefficient of variation or CV%) AUC_{0-24} was 117 (41.2) ng*hr/mL on Day 1, and 204 (28.5) ng*hr/mL on Day 14. Geometric mean (CV %) C_{max} was 7 ng/mL (55.6) on Day 1 and 11 ng/mL (29.3) on day 14. Median time to C_{max} (T_{max}) was 8.0 hours (range 4-24 hours) on Day 1 and 6.0 hours (range 0-16 hours) on Day 14. Accumulation after 14 days of topical application was less than two fold. Trough concentrations generally increased throughout the 14 day study period. Naftifine continued to be detected in plasma in 13/21 (62%) subjects on day 28, the mean (standard deviation or SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range below limit of quantitation (BLQ) to 3 ng/mL). In the same pharmacokinetic trial conducted in patients with tinea pedis and tinea cruris, median fraction of the dose excreted in urine during the treatment period was 0.0016% on Day 1 versus 0.0020% on Day 14.

In a second trial that enrolled 22 subjects, the pharmacokinetics of NAFTIN® Cream was evaluated in 20 pediatric subjects 13 to <18 years of age with both tinea pedis and tinea cruris. Subjects were treated with a median dose of 8.1 g (range 6.6-10.1 g) applied to the affected areas once daily for 2 weeks. The results showed that the systemic exposure increased over the treatment period. Geometric mean (CV%) AUC_{0-24} was 138 (50.2) ng*hr/mL on Day 1, and 192 (74.9) ng*hr/mL on Day 14. Geometric mean (CV %) C_{max} was 9.21 ng/mL (48.4) on Day 1 and 12.7 ng/mL (67.2) on day 14. Median fraction of the dose excreted in urine during the treatment period was 0.0030% on Day 1 and 0.0033% on Day 14.

A third trial evaluated the pharmacokinetics of NAFTIN® Cream in 27 pediatric subjects 2 to < 12 years of age with at least moderate tinea corporis. Subjects were divided into younger (ages 2 to < 6 years, 17 subjects) and older (6 to <12 years, 10 subjects) groups. Median doses of 1.3 g (range 1.0-3.1 g) and 2.3 g (range 2.2-4.2 g) were applied once-daily for 2 weeks in the younger and older groups, respectively, to the affected area plus a ½ inch margin. Plasma and urine pharmacokinetic assessments were conducted on Day 1 in the older group only and on Day 14 in both groups. All subjects showed measurable levels of naftifine in plasma after topical application of NAFTIN® Cream. Following a single dose on Day 1 in subjects 6 to < 12 years of age, the geometric mean (CV%) values of C_{max} and AUC_{0-24} were 3.60 (76.6) ng/mL and 49.8 (64.4) ng*h/mL, respectively. On Day 14 in this group, the C_{max} and AUC_{0-24} were 3.31 (51.2) ng/mL and 52.4

(49.2) ng*h/mL, respectively. In subjects 2 to < 6 years of age on Day 14, the C_{max} and AUC_{0-24} were 3.98 (186) ng/mL and 54.8 (150) ng*h/mL, respectively. In the older group of subjects 6 to 12 years of age, the systemic exposures (both C_{max} and AUC_{0-24}) on Days 1 and 14 were comparable. The median fraction of the dose excreted into urine over 24 hours following drug applications on Day 1 and Day 14 was 0.0029% and 0.0014%, respectively.

12.4 Microbiology

Although the exact mechanism of action against fungi is not known, naftifine hydrochloride appears to interfere with sterol biosynthesis by inhibiting the enzyme squalene2, 3-epoxidase. This inhibition of enzyme activity results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene 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:

Trichophyton rubrum

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year dermal carcinogenicity study, naftifine hydrochloride cream was administered to Sprague-Dawley rats at topical doses of 1%, 2% and 3% (10, 20, and 30 mg/kg/day naftifine hydrochloride). No drug-related tumors were noted in this study up to the highest dose evaluated in this study of 30 mg/kg/day (12 times MRHD based on AUC comparison).

Naftifine hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames 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, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 100 mg/kg/day (6 times MRHD based on mg/m^2 comparison).

14 CLINICAL STUDIES

14.1 Tinea Cruris

NAFTIN® Cream has been investigated for safety and efficacy in a randomized, double-blind, vehicle-controlled, multi-center trial in 146 subjects with symptomatic and dermatophyte culture positive tinea cruris. Subjects were randomized to receive NAFTIN® Cream or vehicle. Subjects applied NAFTIN® Cream or vehicle to the affected area plus a ½-inch margin of healthy skin surrounding the affected area once-daily for 2 weeks. Signs and symptoms of tinea cruris (presence or absence of erythema, pruritus, and scaling) were assessed, and KOH examination and dermatophyte culture were performed at the primary efficacy endpoint at week 4.

The mean age of the trial population was 47 years and 87% were male and 43% were white. At baseline, subjects were confirmed to have signs and symptoms of tinea cruris, positive KOH exam, and confirmed dermatophyte presence based on culture results from a central mycology laboratory. The analysis of the intent-to-treat population was a comparison of the proportions of subjects with a complete cure at the week 4 visit (see Table 1). Complete cure was defined as both clinical cure (absence of erythema, pruritus, and scaling) and mycological cure (negative KOH and dermatophyte culture).

The percentage of subjects experiencing clinical cure and the percentage of subjects experiencing mycological cure at week 4 are presented individually in Table 1 below.

Table 1 Efficacy Results for Tinea Cruris Trial (Week 4 Assessment)

Endpoint	NAFTIN® Cream, 2% N=75	Vehicle N=71
Complete Cure[a]	19 (25%)	2 (3%)
Effective Treatment[b]	45 (60%)	7 (10%)
Mycological Cure[c]	54 (72%)	11 (16%)

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 pruritus grades of 0 or 1 (absent or nearly absent).
c. Mycological cure is defined as negative KOH and dermatophyte culture.

14.2 Interdigital Tinea Pedis

NAFTIN® Cream has been investigated for efficacy in a randomized, double-blind, vehicle-controlled, multi-center trial in 217 subjects with symptomatic and dermatophyte culture positive interdigital tinea pedis. Subjects were randomized to receive NAFTIN® Cream or vehicle. Subjects applied NAFTIN® Cream or vehicle to the affected area of the foot plus a ½-inch margin of healthy skin surrounding the affected area once-daily for 2 weeks. Signs and symptoms of interdigital tinea pedis (presence or absence of erythema, pruritus, and scaling) were assessed and KOH examination and dermatophyte culture was performed at the primary efficacy endpoint at week 6.

The mean age of the trial population was 42 years and 71% were male and 57% were white. 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 proportions of subjects with a complete cure at the week 6 visit (see Table 2). 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 treatment, are presented in Table 2 below. NAFTIN® Cream demonstrated complete cure in subjects with interdigital tinea pedis, but complete cure in subjects with only moccasin type tinea pedis was not demonstrated.

Table 2 Efficacy Results for Interdigital Tinea Pedis Trial (Week 6 Assessment)

Endpoint	NAFTIN® Cream, 2% N=147	Vehicle N=70
Complete Cure[a]	26 (18%)	5 (7%)
Effective Treatment[b]	83 (57%)	14 (20%)
Mycological Cure[c]	99 (67%)	15 (21%)

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

14.3 Tinea Corporis

NAFTIN® Cream has been investigated for safety and efficacy in a randomized, double-blind, vehicle-controlled, multi-center trial in 184 subjects with symptomatic and dermatophyte culture positive tinea corporis. Subjects were randomized to receive NAFTIN® Cream or vehicle. Subjects applied the study agent to all affected body surface areas with tinea corporis plus a ½ inch margin of healthy skin surrounding the affected lesions for two weeks. Signs and symptoms of tinea corporis (presence or absence of erythema, induration, and pruritus) were assessed and KOH examination and dermatophyte culture were performed for the assessment of primary efficacy endpoint at Day 21.

The trial population was pediatric (≥2 to <18 years of age) with a median age of 9 years (NAFTIN® Cream) or 8 years (vehicle); 61% of subjects were male and 45% were white. At baseline, subjects were confirmed to have signs and symptoms of tinea corporis, positive KOH exam, and confirmed dermatophyte culture. The primary efficacy endpoint was the proportions of subjects with a complete cure at the Day 21 visit. Complete cure was defined as both a clinical cure (absence of erythema, induration, and pruritus on all lesions present at baseline) and mycological cure (negative KOH and dermatophyte culture).

The efficacy results at Day 21, one week following the end of treatment, are presented in Table 3 below.

Table 3 Efficacy Results for Pediatric Tinea Corporis Trial (Day 21 Assessment)

Endpoint	NAFTIN® Cream, 2% N=91	Vehicle N=93
Complete Cure[a]	42 (46%)	26 (28%)
Effective Treatment[b]	53 (58%)	32 (34%)
Mycological Cure[c]	57 (63%)	36 (39%)

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
NAFTIN® Cream, 2%, is a white to off-white cream supplied in collapsible tubes in the following sizes: 30g – NDC 54766-102-30
45g – NDC 54766-102-45
60g – NDC 54766-102-60

Storage
Store NAFTIN® Cream 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® Cream is for topical use only. NAFTIN® Cream is not intended for oral, intravaginal or ophthalmic use.
- If irritation or sensitivity develops with the use of NAFTIN® Cream treatment should be discontinued and appropriate therapy instituted. Patients should be directed to contact their physician if these conditions develop following use of NAFTIN® Cream.

Distributed By Sebela Pharmaceuticals Inc.
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Rev. 04/2018

PI10245001

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NAFTIN® Gel, 2% safely and effectively. See full prescribing information for NAFTIN® (naftifine hydrochloride) Gel, 2%.

NAFTIN® (naftifine hydrochloride) Gel, 2% 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)

----------ADVERSE REACTIONS----------

The most common adverse reactions are application site reactions (2%). (6.1)

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: 04/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 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*.

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 colorless to yellow gel.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Adverse Reactions

If irritation or sensitivity develops with the use of NAFTIN® Gel, treatment should be discontinued.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In two randomized, vehicle-controlled trials, 1143 subjects were treated with NAFTIN® Gel versus 571 subjects treated with the 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. The following adverse reactions have been identified during post-approval use of naftifine hydrochloride: blisters, burning sensation, crusting, dryness, erythema/redness, inflammation, irritation, maceration, pain, pruritus [mild]/itching, rash and swelling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There are no adequate and well-controlled trials of NAFTIN® Gel in pregnant women. Because animal reproduction studies are not always predictive of human response, NAFTIN® Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The animal multiples of human exposure calculations were based on daily dose body surface area comparison (mg/m^2) for the reproductive toxicology studies described in this section and in Section 13.1. The Maximum Recommended Human Dose (MRHD) was set at 4 g 2% gel per day (1.33 mg/kg/day for a 60 kg individual).

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 30, 100, and 300 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at doses up to 300 mg/kg/day (36.5X MRHD). Subcutaneous doses of 10 and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day (3.7X MRHD). Subcutaneous doses of 3, 10, and 30 mg/kg/day naftifine hydrochloride were administered during the period of organogenesis (gestational days 6 – 18) to pregnant female rabbits. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day (7.3X MRHD).

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 the offspring during lactation was noted at 300 mg/kg/day (36.5X MRHD). No developmental toxicity was noted at 100 mg/kg/day (12.2X MRHD).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NAFTIN® Gel is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of NAFTIN® Gel have been established in the age group 12-18 with interdigital tinea pedis.
Use of NAFTIN® Gel in this age group is supported by evidence from adequate and well controlled studies in adults with additional safety and PK data from an open label trial, conducted in 22 adolescents ≥12 years of age who were exposed to NAFTIN® Gel at a dose of approximately 4 g/day *[see Clinical Pharmacology (12.3)]*.

Safety and effectiveness in pediatric patients <12 years of age have not been established.

8.5 Geriatric Use

During clinical trials, 99 subjects (9%) aged 65 years and over were exposed to NAFTIN® Gel. Safety and effectiveness were similar to those reported by younger ~~patients~~subjects.

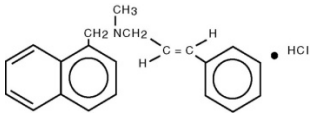
11 DESCRIPTION

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 $C_{21}H_{21}N$•HCl with a molecular weight of 323.86.

The structural formula of naftifine hydrochloride is:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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%) AUC_{0-24} (area under plasma concentration-versus-time curve from time 0 to 24 hours) of 10.5 (118) ng•hr/mL on Day 1 and an AUC_{0-24} 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 T_{max} was 20.0 hours (range: 8, 20 hours) after a single application on Day 1 and 8.0 hours (range: 0, 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 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%) Cmax 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 squalene 2, 3-epoxidase. The inhibition of enzyme activity by this allylamine results in decreased amounts of sterols, especially ergosterol, and a corresponding accumulation of squalene 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:

Trichophyton rubrum
Trichophyton mentagrophytes
Epidermophyton floccosum

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year dermal carcinogenicity study, naftifine hydrochloride cream was administered to Sprague-Dawley rats at topical doses of 1%, 2% and 3% (10, 20, and 30 mg/kg/day naftifine hydrochloride). No drug-related tumors were noted in this study up to the highest dose evaluated in this study of 30 mg/kg/day (36 times MRHD based on AUC comparison).

Naftifine hydrochloride revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames 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, throughout mating, gestation, parturition, and lactation, demonstrated no effects on growth, fertility, or reproduction, at doses up to 100 mg/kg/day (12 times MRHD based on mg/m^2 comparison).

14 CLINICAL STUDIES

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 Latino. 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 treatment, are presented in Table 1 below. NAFTIN® Gel demonstrated complete cure in subjects with interdigital type tinea pedis.

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 Treatment Failure)

	Trial 1		Trial 2	
Endpoint	NAFTIN® Gel, 2% N=382 n (%)	Vehicle N=179 n (%)	NAFTIN® Gel, 2% N=400 n (%)	Vehicle N=213 n (%)
Complete Cure[a]	64 (17%)	3 (2%)	104 (26%)	7 (3%)
Treatment Effectiveness[b]	207 (54%)	11 (6%)	203 (51%)	15 (7%)
Mycological Cure[c]	250 (65%)	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 pruritus 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 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.

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Rev. 04/2018
PI77260001