

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204286Orig1s000

LABELING

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 (naftifine hydrochloride) Gel, 2% is an allylamine antifungal indicated for the treatment of interdigital tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients 18 years of age and older. (1)

-----**DOSAGE AND ADMINISTRATION**-----

Apply a thin layer of NAFTIN (naftifine hydrochloride) Gel, 2% 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 (naftifine hydrochloride) Gel, 2% 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, 2% 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 Merz Pharmaceuticals, LLC at 877-743-8454 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NAFTIN (naftifine hydrochloride) Gel, 2% is an allylamine antifungal indicated for the treatment of interdigital tinea pedis caused by the organisms *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* in patients 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

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

For topical use only. NAFTIN (naftifine hydrochloride) Gel, 2% 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 (naftifine hydrochloride) Gel, 2%, 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 practice.

In two randomized, vehicle-controlled trials, 1143 subjects were treated with NAFTIN (naftifine hydrochloride) Gel, 2% 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 (naftifine hydrochloride) Gel, 2% arm versus 1% in vehicle arm. Most adverse reactions were mild in severity.

Cumulative irritancy testing revealed the potential for NAFTIN (naftifine hydrochloride) Gel, 2% to cause irritation. There was no evidence that NAFTIN (naftifine hydrochloride) Gel, 2% 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 postmarketing 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

Pregnancy Category B. There are no adequate and well-controlled trials of NAFTIN (naftifine hydrochloride) Gel, 2% in pregnant women. Because animal reproduction studies are not always predictive of human response, NAFTIN (naftifine hydrochloride) Gel, 2% 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 $\text{mg}/\text{kg}/\text{day}$ for a 60 kg individual).

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 30, 100, and 300 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$ (36.5X MRHD). Subcutaneous doses of 10 and 30 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$ (3.7X MRHD). Subcutaneous doses of 3, 10, and 30 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$ (7.3X MRHD).

A peri- and post-natal development study was conducted in rats. Oral doses of 30, 100, and 300 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$ (36.5X MRHD). No developmental toxicity was noted at 100 $\text{mg}/\text{kg}/\text{day}$ (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 (naftifine hydrochloride) Gel, 2% is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. The number of pediatric subjects \leq 12 years of age studied was too small to adequately assess safety and efficacy.

8.5 Geriatric Use

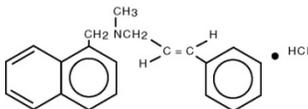
During clinical trials, 99 subjects (9%) aged 65 years and over were exposed to NAFTIN Gel, 2%. Safety and effectiveness were similar to those reported by younger patients.

11 DESCRIPTION

NAFTIN (naftifine hydrochloride) Gel, 2% is a clear to yellow gel for topical use only. Each gram of NAFTIN (naftifine hydrochloride) Gel, 2% contains 20 mg of naftifine hydrochloride, a synthetic allylamine antifungal compound.

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

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



The structural formula of naftifine hydrochloride is:

NAFTIN (naftifine hydrochloride) Gel, 2% contains the following inactive ingredients: alcohol, benzyl alcohol, edentate disodium, hydroxyethyl cellulose, purified water, propylene glycol, polysorbate 20 and trolamine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NAFTIN (naftifine hydrochloride) Gel, 2% is a topical antifungal drug [see *Clinical Pharmacology* (12.4)].

12.2 Pharmacodynamics

The pharmacodynamics of NAFTIN (naftifine hydrochloride) Gel, 2% 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 tinea pedis subjects treated with a mean dose of 3.9 grams NAFTIN (naftifine hydrochloride) Gel, 2% 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 was less than or equal to 0.01% 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 described.

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

Long-term studies to evaluate the carcinogenic potential of NAFTIN (naftifine hydrochloride) Gel, 2% have not been performed.

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 (12.2X MRHD).

14 CLINICAL STUDIES

NAFTIN (naftifine hydrochloride) Gel, 2% has been evaluated for efficacy in two randomized, double-blind, vehicle-controlled, multicenter trials that included 1175 subjects with symptomatic and dermatophyte culture-positive tinea pedis. Subjects were randomized to receive NAFTIN (naftifine hydrochloride) Gel, 2% 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 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 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, 2% (Full Analysis Set, Missing Values Treated as Treatment Failure)

Endpoint	Trial 1		Trial 2	
	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 (naftifine hydrochloride) Gel, 2% is a colorless to yellow gel supplied in collapsible tubes in the following size:
45g – NDC 0259-1202-45

Storage

Store NAFTIN (naftifine hydrochloride) Gel, 2% at 25 C (77 F); excursions permitted to 15-30 C (59-86 F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

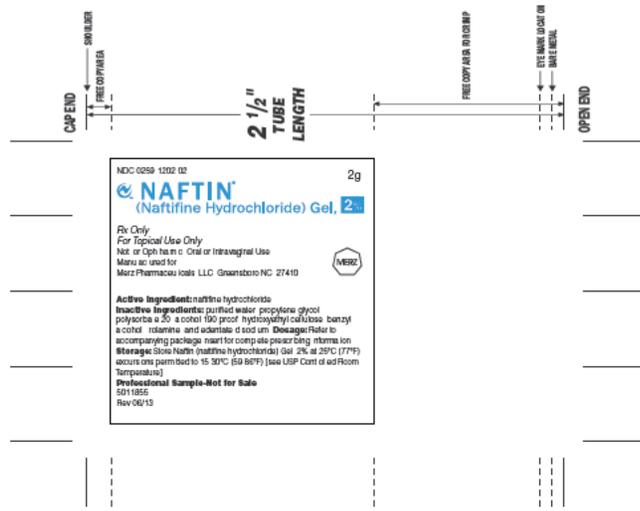
- Inform patients that NAFTIN (naftifine hydrochloride) Gel, 2% is for topical use only. NAFTIN (naftifine hydrochloride) Gel, 2% is not intended for ophthalmic, oral, or intravaginal use.
- Patients should be directed to contact their physician if irritation develops with the use of NAFTIN (naftifine hydrochloride) Gel, 2% .

NAFTIN (naftifine hydrochloride) Gel, 2% is manufactured for Merz Pharmaceuticals, LLC, Greensboro, NC 27410.

NAFTIN (naftifine hydrochloride) is a registered trademark of Merz Pharmaceuticals, LLC.







NDC 0259-1102-02 2g

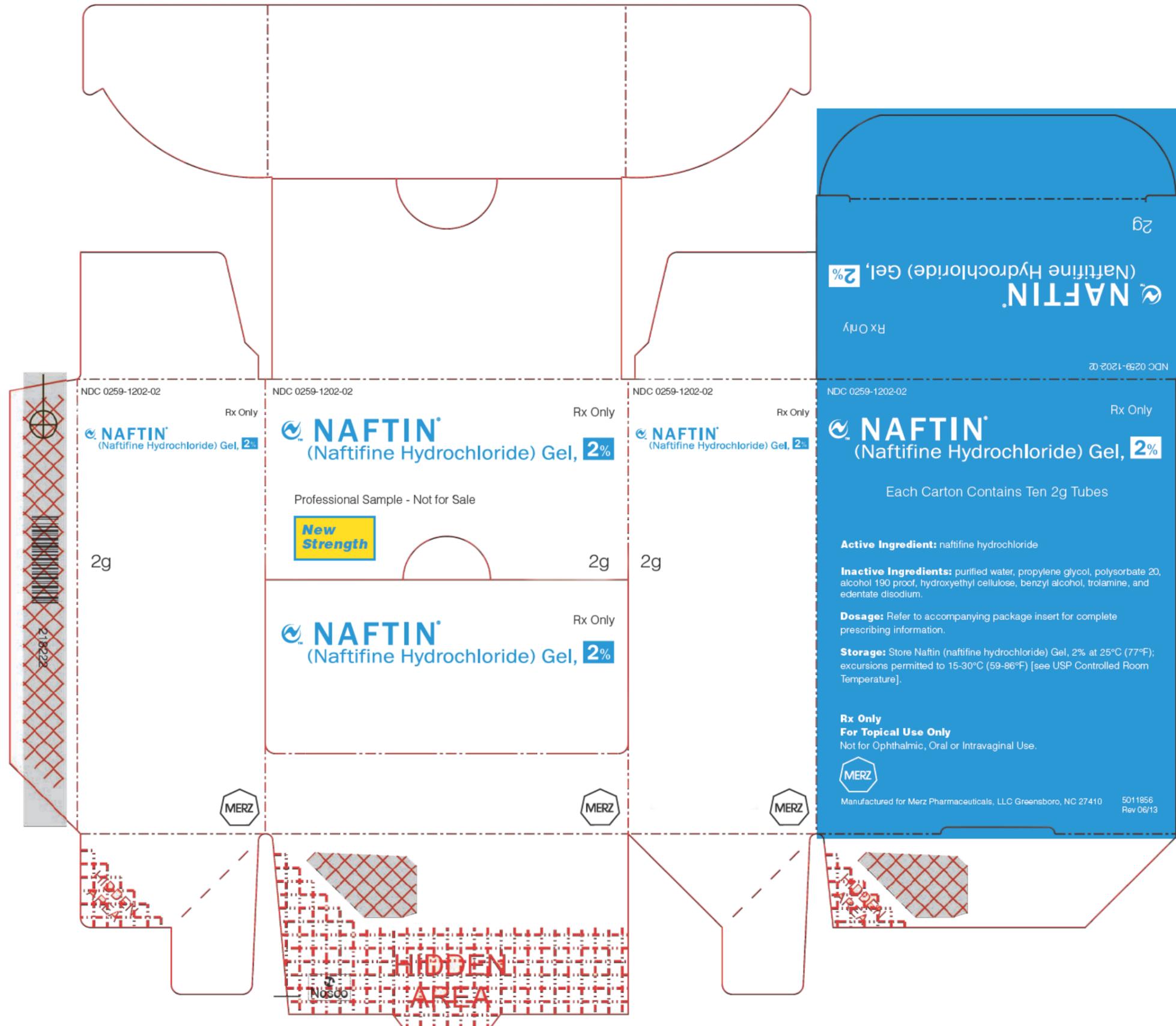
NAFTIN
(Naftifine Hydrochloride) Gel, 2g

Rx Only
For Topical Use Only
Not for Ophthalmic, Oral or Intravaginal Use
Manufactured for
Merz Pharmaceuticals LLC, Gannettville NC 27410

Active Ingredients: naftifine hydrochloride
Inactive Ingredients: purified water, propylene glycol, polyacrylate 50, acohol, 190 proof, hydroxyethylcellulose, benzyl alcohol, niacinamide, and sorbitol. See package insert to accompanying package insert for complete prescribing information.

Storage: Store Naftin (naftifine hydrochloride) Gel, 2% at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Professional Sample-Not for Sale
SFI1955C
Rev 06/13



NDC 0259-1202-02

Rx Only

NAFTIN
(Naftifine Hydrochloride) Gel, 2%

2g

218222



NDC 0259-1202-02

Rx Only

NAFTIN
(Naftifine Hydrochloride) Gel, 2%

Professional Sample - Not for Sale

New Strength

2g

NAFTIN
(Naftifine Hydrochloride) Gel, 2%

Rx Only



NDC 0259-1202-02

Rx Only

NAFTIN
(Naftifine Hydrochloride) Gel, 2%

2g



NDC 0259-1202-02

Rx Only

NAFTIN
(Naftifine Hydrochloride) Gel, 2%

Each Carton Contains Ten 2g Tubes

Active Ingredient: naftifine hydrochloride

Inactive Ingredients: purified water, propylene glycol, polysorbate 20, alcohol 190 proof, hydroxyethyl cellulose, benzyl alcohol, tolamine, and edentate disodium.

Dosage: Refer to accompanying package insert for complete prescribing information.

Storage: Store Naftin (naftifine hydrochloride) Gel, 2% at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx Only
For Topical Use Only
Not for Ophthalmic, Oral or Intravaginal Use.



Manufactured for Merz Pharmaceuticals, LLC Greensboro, NC 27410

5011856
Rev 06/13

Not for Sale

HIDDEN AREA

2g

NAFTIN
(Naftifine Hydrochloride) Gel, 2%

Rx Only

NDC 0259-1202-02

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/s/

SUSAN J WALKER
06/27/2013