

NAFTIFINE HYDROCHLORIDE- naftifine hydrochloride cream
Renaissance Pharma, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Naftifine Hydrochloride Cream, 2% safely and effectively.

See full prescribing information for Naftifine Hydrochloride Cream, 2%.

Naftifine Hydrochloride Cream, 2% for topical use

Initial U.S. Approval: 1988

----- **INDICATIONS AND USAGE** -----

Naftifine Hydrochloride Cream, 2% 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. Naftifine Hydrochloride Cream, 2% is not for ophthalmic, oral, or intravaginal use. (2)

Apply a thin layer of Naftifine Hydrochloride Cream, 2% 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** -----

If redness or irritation develops with the use of Naftifine Hydrochloride Cream, 2% treatment should be discontinued. (5.1)

----- **ADVERSE REACTIONS** -----

The most common adverse reaction (≥1%) is pruritus. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Renaissance Pharma, Inc at 1-877-622-2334 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

3 DOSAGE FORMS AND STRENGTHS

Cream: 2%, white to off-white cream

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Local Adverse Reactions

If irritation or sensitivity develops with the use of Naftifine Hydrochloride Cream, 2% treatment should be discontinued. Patients should be directed to contact their physician if these conditions develop following use of Naftifine Hydrochloride Cream, 2%.

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.

During clinical trials, 760 subjects were exposed to naftifine 1% and 2% cream formulations. A total of 421 subjects with tinea pedis and/or tinea cruris were treated with Naftifine Hydrochloride Cream, 2%. In two randomized, vehicle-controlled trials (400 patients were treated with Naftifine Hydrochloride Cream, 2%. 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 Naftifine Hydrochloride Cream, 2% treated subjects experienced an adverse reaction compared with 19.3% of vehicle subjects. The most common adverse reaction ($\geq 1\%$) is pruritus. Most adverse reactions were mild in severity. The incidence of Adverse Reactions in the Naftifine Hydrochloride Cream, 2% treated population were not significantly different than the vehicle treated population.

In an open-label pediatric pharmacokinetics and safety trial, 22 pediatric subjects 13-17 years of age with interdigital tinea pedis and tinea cruris received Naftifine Hydrochloride Cream, 2%. 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 postmarketing 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

Pregnancy Category B. There are no adequate and well-controlled studies of Naftifine Hydrochloride Cream, 2% in pregnant women. Because animal reproduction studies are not always predictive of human response, Naftifine Hydrochloride Cream, 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 8 g 2% cream per day (2.67 $\text{mg}/\text{kg}/\text{day}$ 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 $\text{mg}/\text{kg}/\text{day}$ (18.2 \times 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 $\text{mg}/\text{kg}/\text{day}$ (1.8 \times 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 $\text{mg}/\text{kg}/\text{day}$ (3.6 \times 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 $\text{mg}/\text{kg}/\text{day}$ (18.2 \times MRHD). No developmental toxicity was noted at 100 $\text{mg}/\text{kg}/\text{day}$ (6.1 \times 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 Naftifine Hydrochloride Cream, 2% is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Naftifine Hydrochloride Cream, 2% have been established in the age group 12-17 with interdigital tinea pedis and tinea cruris. Use of Naftifine Hydrochloride Cream, 2% 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 Naftifine Hydrochloride Cream, 2% at a dose of approximately 8 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

Clinical studies of Naftifine Hydrochloride Cream, 2% did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

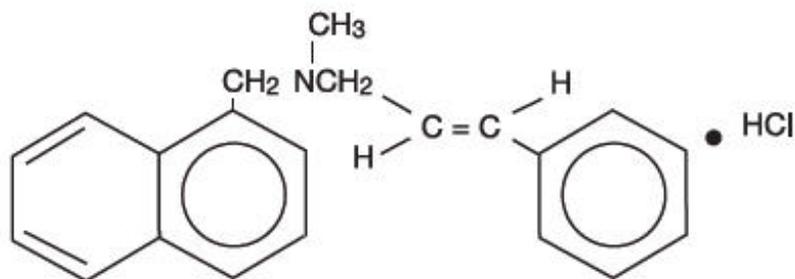
11 DESCRIPTION

Naftifine Hydrochloride Cream, 2% is a white to off-white cream for topical use only. Each gram of (naftifine hydrochloride) Cream 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:



Naftifine Hydrochloride Cream, 2% 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

Naftifine Hydrochloride Cream, 2% is a topical antifungal drug [see *Clinical Pharmacology*(12.4)]

12.2 Pharmacodynamics

The pharmacodynamics of Naftifine Hydrochloride Cream, 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.

The pharmacokinetics of Naftifine Hydrochloride Cream, 2% was evaluated following once-daily topical application for 2 weeks to twenty one 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 (AUC)) to naftifine increased over the 2 week treatment period in all the 21 subjects. Geometric Mean (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 T_{max} was 8.0 hours on Day 1 (range: 4 to 24) and 6.0 hours on Day 14 (range: 0 to 16). 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 (SD) plasma concentrations were 1.6 ± 0.5 ng/mL (range below limit of quantitation (BLQ) to 3 ng/mL).

In the same pharmacokinetic study 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 Naftifine Hydrochloride Cream, 2% was evaluated in 20 pediatric subjects 13 – 17 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 14 days. 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.

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 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.

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

Long-term studies to evaluate the carcinogenic potential of Naftifine Hydrochloride Cream, 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 ($6.1 \times$ MRHD).

14 CLINICAL STUDIES

14.1 Tinea Cruris

Naftifine Hydrochloride Cream, 2% has been investigated for safety and efficacy in a randomized, double-blind, vehicle-controlled, multi-center study in 146 subjects with symptomatic and dermatophyte culture positive tinea cruris. Subjects were randomized to receive (naftifine hydrochloride) Cream or vehicle. Subjects applied the study agent (naftifine hydrochloride) 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 study 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 Pivotal Tinea Cruris Trial (Week 4 Assessment)

Endpoint	Naftifine hydrochloride cream, 2% N=75	Vehicle N=71
Complete Cure*	19(25%)	2(3%)
Effective Treatment†	45(60%)	7(10%)
Mycological Cure‡	54(72%)	11(16%)

* 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).

† Effective treatment is a negative KOH preparation and negative dermatophyte culture, erythema, scaling, and pruritus grades of 0 or 1 (absent or nearly absent).

‡ Mycological cure is defined as negative KOH and dermatophyte culture.

14.2 Interdigital Tinea Pedis

Naftifine Hydrochloride Cream, 2% has been investigated for efficacy in a randomized, double-blind, vehicle-controlled, multi-center study in 217 subjects with symptomatic and dermatophyte culture positive tinea pedis. Subjects were randomized to receive Naftifine Hydrochloride Cream, 2% or vehicle. Subjects applied the study agent (naftifine hydrochloride) 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 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 study population was 42 years and 71% were male and 57% were white. 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 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. Naftifine Hydrochloride Cream, 2% 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 Pivotal Tinea Pedis Trial (Week 6 Assessment)

Endpoint	Naftifine hydrochloride cream, 2% N=147	Vehicle N=70
Complete Cure*	26(18%)	5(7%)
Effective Treatment†	83(57%)	14(20%)
Mycological Cure‡	99(67%)	15(21%)

* 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).

† Effective treatment is a negative KOH preparation and negative dermatophyte culture, erythema, scaling, and pruritus grades of 0 or 1 (absent or near absent).

‡ Mycological cure is defined as negative KOH and dermatophyte culture.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Naftifine Hydrochloride Cream, 2% is a white to off-white cream supplied in collapsible tubes in the following sizes:

30g – NDC 40085-203-30

45g – NDC 40085-203-45

60g – NDC 40085-203-60

Storage

Store Naftifine Hydrochloride Cream, 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 Naftifine Hydrochloride Cream, 2% is for topical use only. Naftifine Hydrochloride Cream, 2% is not intended for intravaginal or ophthalmic use.
- If irritation or sensitivity develops with the use of Naftifine Hydrochloride Cream, 2% treatment should be discontinued and appropriate therapy instituted. Patients should be directed to contact their physician if these conditions develop following use of Naftifine Hydrochloride Cream, 2%.

Manufactured for Renaissance Pharma, Inc,
Newtown, PA 18940

Manufactured by DPT Laboratories, Ltd.,
San Antonio, Tx 78215

140732

Rev. 01/2016

PRINCIPAL DISPLAY PANEL - 45 g Tube Carton

Naftifine Hydrochloride Cream, 2%

NDC 40085-203-45

For Topical Use Only

Not for Ophthalmic,
Oral or Intravaginal Use

**Renaissance
Pharma**

**45 g Cream
Rx Only**



NAFTIFINE HYDROCHLORIDE

naftifine hydrochloride cream

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:40085-203
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NAFTIFINE HYDROCHLORIDE (UNII: 25UR9N9041) (NAFTIFINE - UNII:4FB1TON47A)	NAFTIFINE HYDROCHLORIDE	20 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
BENZYL ALCOHOL (UNII: LKG8494WBH)	
CETYL ALCOHOL (UNII: 936JST6JCN)	
CETYL ESTERS WAX (UNII: D072FFP9GU)	
ISOPROPYL MYRISTATE (UNII: 0RE8K4LNJS)	
POLYSORBATE 60 (UNII: CAL22UVI4M)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
SORBITAN MONOSTEARATE (UNII: NVZ4I0H58X)	
STEARYL ALCOHOL (UNII: 2KR89I4HIY)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:40085-203-45	1 in 1 CARTON	02/01/2016	08/31/2021
1		45 g in 1 TUBE; Type 0: Not a Combination Product		
2	NDC:40085-203-60	1 in 1 CARTON	02/01/2016	09/30/2020
2		60 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019599	02/01/2016	08/31/2021

Labeler - Renaissance Pharma, Inc. (078290398)

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Renaissance Pharma, Inc.