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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 204286
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Product: NAFTIN (naftifine hydrochloride) Gel, 2%
Indication: Tinea pedis
Applicant: Merz pharmaceuticals, Greensboro, NC
Review Division: Dermatology and Dental Products
Reviewer: Jianyong Wang, PhD
Supervisor/Team Leader: Barbara Hill, PhD
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1 Executive Summary

1.1 Introduction

Naftifine hydrochloride is a synthetic allylamine derivative. The antifungal activity of naftifine HCl is likely related to its inhibition of squalene epoxidase in dermatophytes, leading to an accumulation of intracellular lipids that ultimately results in irreversible damage to the fungal cell wall. Naftifine HCl is the active ingredient of NAFTIN[®] Cream, 1% and 2%, and NAFTIN[®] Gel, 1%. NAFTIN[®] Cream, 1% (NDA 19599) and NAFTIN[®] Gel, 1% (NDA 19356) were approved for the treatment of tinea pedis, tinea cruris, and tinea corporis on 02/29/1988 and 06/18/1990, respectively. NAFTIN[®] Cream, 2% (code name: NAFT-500), approved on 01/13/2012 for the treatment of tinea pedis, tinea cruris, and tinea corporis (NDA 19599 Supplement-11), provides shorter treatment duration over the 1% cream product. The sponsor submitted NDA 204286 to pursue marketing approval of NAFTIN[®] Gel, 2% (code name: NAFT-600), for the treatment of tinea pedis. NAFTIN[®] Gel, 2%, would also provide shorter treatment duration over the 1% gel product.

The sponsor references nonclinical information contained in NDA 19599 to support this NDA. There were no new nonclinical data submitted to this NDA. A 2-year dermal rat carcinogenicity study will be conducted as a postmarketing requirement (PMR), which was stated in the approval letter for NDA 19599 S-11.

1.2 Brief Discussion of Nonclinical Findings

Naftifine HCl had an apparent stimulating effect on the central nervous system in mice and rats. Naftifine had a very weak effect on the cardiovascular system of anesthetized cats. During IV infusion, the reduction in mean arterial blood pressure and heart rate, carotid occlusion, and nictitating membrane responses were noted; however, such findings were still within the historical control range. No signs of toxicity or ECG changes were observed up to a cumulative IV dose of 18.7 mg/kg. In anesthetized dogs, no significant effects on the cardiovascular parameters, ECG, or diuresis were noted following an intra-arterial dose of 0.005 mg/kg or intraduodenal doses up to 5 mg/kg. A slight increase in heart rate was noted at the 5 mg/kg intraduodenal dose as compared with control.

General toxicology studies have been conducted extensively with various formulations of naftifine HCl in rats, rabbits, guinea pigs, dogs, monkeys, and minipigs. Findings in oral toxicity studies included reduction in body weight gain and increases in serum bilirubin, creatinine, and urea levels. Findings in dermal toxicity studies included very slight erythema and reduction in body weight gain.

In genetic toxicology studies, naftifine HCl was negative in a bacterial mutagenicity test, an *in vitro* chromosome aberration test, and an *in vivo* micronucleus test. There is no concern for the genotoxicity of naftifine HCl.

To date there is no carcinogenicity data available for naftifine HCl. The Agency requests only one of the two products (NAFT-500 or NAFT-600) be tested for carcinogenicity to address the concern for carcinogenic potential of naftifine HCl. It is acceptable for the sponsor to conduct a 2-year dermal rat carcinogenicity study with the cream formulation. A carcinogenicity study protocol was reviewed by the Executive CAC on 01/22/2013 and the proposed doses received concurrence from the Committee. The final carcinogenicity study report should be submitted by 09/2016.

Reproductive and developmental toxicology studies have been conducted with naftifine HCl in rats and rabbits. Naftifine HCl did not affect fertility in rats at oral doses up to 100 mg/kg/day. Naftifine HCl did not show a teratogenic effect in rats at oral doses up to 300 mg/kg/day or in rabbits at subcutaneous doses up to 30 mg/kg/day. No treatment-related effects on embryofetal toxicity or teratogenicity were noted in rats at subcutaneous doses up to 30 mg/kg/day. Naftifine HCl had no adverse effects on peri- and post-natal development in rats at oral doses up to 100 mg/kg/day.

Naftifine HCl solutions up to 10% were not irritating to rabbit skin. Naftifine HCl 5% solution was not a contact sensitizer in guinea pigs. Naftifine HCl and NAFT-600 gel exhibited minimal UVB absorbance. The extent of UVB absorbance does not trigger the need for a nonclinical phototoxicity study.

Overall the toxicity profile of NAFT-600 drug product has been well characterized. There was no significant safety concern for the inactive ingredients contained in the NAFT-600 product. The proposed daily topical dosage of NAFT-600 (2% gel applied once daily) would be comparable to the approved dosage of NAFTIN[®] Gel, 1% (applied twice daily). The maximum recommended human dose (MRHD) for NAFTIN[®] Gel, 2%, was 4 g gel per day (80 mg/day naftifine HCl), which is half of the MRHD for NAFTIN[®] Cream, 2% (8 g cream per day, 160 mg/day naftifine HCl) due to indication difference (tinea pedis only vs. tinea pedis, tinea cruris, and tinea corporis). Because TK data were not obtained in most toxicology studies, the multiples of human exposure were calculated based on BSA comparison, assuming 100% absorption after dermal application. It should be noted that such calculated multiples are very conservative if derived from systemic toxicology studies in which test article was administered via gavage or subcutaneous injection. From a pharmacology/toxicology perspective, the proposed clinical dose for NAFTIN[®] Gel, 2%, does not cause significant safety concern.

1.3 Recommendations

1.3.1 Approvability

NDA 204286 is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the label for NAFTIN[®] Gel, 2%.

1.3.2 Additional Nonclinical Recommendations

A 2-year dermal rat carcinogenicity study will be conducted as a PMR (see Section 8 for details).

1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the NAFTIN® Gel 2% label reproduced below. The pharmacologic class designation for naftifine hydrochloride (i.e., allyamine antifungal) is correct.

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 $\text{mg}/\text{kg}/\text{day}$ (36.5 ^{(b)(4)} X 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 $\text{mg}/\text{kg}/\text{day}$ (3.7 ^{(b)(4)} X 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 $\text{mg}/\text{kg}/\text{day}$ (7.3 ^{(b)(4)} X 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 $\text{mg}/\text{kg}/\text{day}$ (36.5 ^{(b)(4)} X MRHD). No developmental toxicity was noted at 100 $\text{mg}/\text{kg}/\text{day}$ (12.2 ^{(b)(4)} X MRHD).

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* ^{(b)(4)} genotoxicity tests (Ames assay and Chinese

hamster ovary cell chromosome aberration assay) and one *in vivo* (b) (4) 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 (12.2 (b) (4) X MRHD).

2 Drug Information

2.1 Drug

CAS Registry Number: 65473-14-5

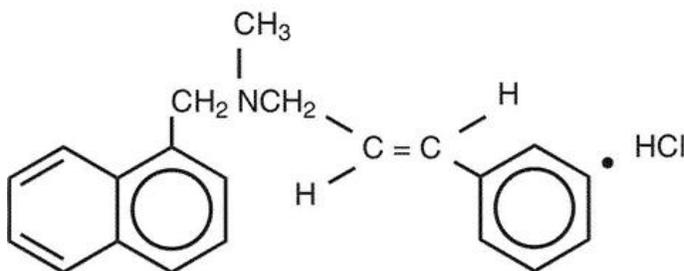
Generic Name: Naftifine hydrochloride 2% gel

Code Name: NAFT-600, SN 105-843

Chemical Name: (E)-N-Cinnamyl-N-methyl-1-naphthatenemethylamine hydrochloride

Molecular Formula/Molecular Weight: C₂₁H₂₁N•HCl / 323.86

Structure or Biochemical Description:



Pharmacologic Class: Allylamine Antifungal (Note: This is an established pharmacologic class.)

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 77530 [NAFT-500 (naftifine hydrochloride 2% cream), active, DDDP]
- IND 105603 [NAFT-600 (naftifine hydrochloride 2% gel), active, DDDP]
- IND (b) (4)
- IND 22919 [Naftin (naftifine hydrochloride) Cream, 1%, active, DDDP]
- NDA 19356 [Naftin (naftifine hydrochloride) Gel, 1%, approved, DDDP]
- NDA 19599 [Naftin (naftifine hydrochloride) Cream, 1% and 2%, approved, DDDP]

2.3 Drug Formulation

The composition of NAFTIN[®] Gel, 2%, is listed in the following table (copied from submission).

Table 1 Composition of NAFT-600 Gel, 2%

Component	Reference	Concentration (% w/w)	Function
Naftifine hydrochloride	USP	2.00	Active Ingredient
(b) (4)	USP		
Propylene Glycol	USP		
Polysorbate 20	NF		
Alcohol (b) (4)	USP		
Hydroxyethyl Cellulose	NF		
Benzyl Alcohol	NF		
Trolamine	NF		
Edetate Disodium	USP		

NF=National Formulary, USP=United States Pharmacopeia

The sponsor modified the formulation of NAFTIN[®] Gel, 2% (mainly lowered the concentration of alcohol) with an intension to reduce irritation, compared to NAFTIN[®] Gel, 1%.

The comparison of the composition of NAFTIN[®] Gel 2% and 1% is shown in the following table (the composition of the 1% gel formulation was obtained from the Pre-Phase 3 meeting briefing document).

Component	Grade	NAFTIN [®] Gel 2% (% w/w)	NAFTIN [®] Gel 1% (% w/w)
Naftifine hydrochloride	USP	2.00	1.00
(b) (4)	USP		
Alcohol (b) (4)	USP		
Edetate Disodium	USP		
Propylene glycol	USP		
Polysorbate 20	NF		
Hydroxyethyl cellulose	NF		
Benzyl alcohol	NF		
Trolamine	NF		
(b) (4)	NF		
Polysorbate 80	NF		
(b) (4)	NF		

NF: National Formulary; USP: United States Pharmacopeia

2.4 Comments on Novel Excipients

There are no novel excipients in the NAFTIN[®] Gel 2% formulation. All excipients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products. There are no significant safety concerns for the excipients contained in NAFTIN[®] Gel, 2%.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

NAFTIN[®] Gel, 2% is indicated for the treatment of tinea pedis in patients 18 years of age and older.

NAFTIN[®] Gel, 2% should be applied to the affected areas plus an approximate ½ inch margin of healthy surrounding skin once daily for 2 weeks. Under the maximum clinical use condition, the maximum topical dose of NAFTIN[®] Gel, 2% would be 4 g/day for 2 weeks (1.33 mg/kg/day naftifine HCl for a 60 kg individual).

2.7 Regulatory Background

NAFTIN[®] 1% Cream and NAFTIN[®] 1% Gel were approved under NDA 19599 (on 02/29/1988) and NDA 19356 (on 06/18/1990), respectively, for the treatment of tinea pedis, tinea cruris, and tinea corporis. NAFTIN[®] Cream, 2% (code name: NAFT-500), was approved on 01/13/2012 for the treatment of tinea pedis, tinea cruris, and tinea corporis (NDA 19599 Supplement-11). NAFTIN[®] Cream, 2% provides shorter treatment duration (once daily for two weeks) over the 1% cream product (once daily for up to 4 weeks). The sponsor submitted this NDA to pursue marketing approval of NAFTIN[®] Gel, 2% (code name: NAFT-600), for the treatment of tinea pedis. NAFTIN[®] Gel, 2%, would also provide shorter treatment duration (once daily for two weeks) over the 1% gel product (twice daily for up to 4 weeks).

3 Studies Submitted

None. The sponsor references nonclinical information contained in NDA 19599 to support this NDA. There were no new nonclinical data submitted to this NDA. All the submitted pivotal toxicology studies were reviewed previously by FDA.

3.3 Previous Reviews Referenced

- IND [REDACTED] (b) (4)
- IND 77530 nonclinical reviews (by this reviewer, 06/30/2008, 01/27/2011, and 01/23/2013)
- IND 105603 nonclinical review (by this reviewer, 06/17/2009)
- NDA 19599 S-11 nonclinical review (by this reviewer, 08/01/2011)

4 Pharmacology

4.1 Primary Pharmacology

Naftifine HCl is a synthetic allylamine derivative. It is an antifungal agent that acts by inhibiting squalene epoxidase, a key enzyme involved in fungal cell reproduction.

Inhibition of squalene epoxidase results in the accumulation of squalene that is associated with intracellular degenerative processes, such as the deposition of lipid droplets. This accumulation occurs in the cell membrane as well as other membranes (i.e., the endoplasmic reticulum). Alterations in membrane properties will lead to cell wall damage, which explains the fungicidal action.

In vitro studies have demonstrated that naftifine HCl is effective against several strains of dermatophytes, including *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton violaceum* spp., *Microsporum canis* sp., and *Epidermophyton floccosum*. Naftifine HCl also showed efficacy in guinea pigs infected with *T. mentagrophytes*.

4.2 Secondary Pharmacology

Naftifine HCl exhibits bactericidal and anti-inflammatory activity, though the exact mechanism of action is unclear.

4.3 Safety Pharmacology

In mice and rats, naftifine had an apparent stimulating effect on the central nervous system following single oral doses (32-320 mg/kg in mice and 10-100 mg/kg in rats), which appeared after a latency period. Naftifine at 50 mg/kg (i.p.) did not have significant effects on apomorphine-induced gnawing behavior or tetrabenazine-induced catalepsy in mice.

Naftifine had a very weak effect on the cardiovascular system of anesthetized cats when administered in increasing IV doses (4-500 mg/kg/min) over a 2-hr period. During drug infusion, there were reduction in mean arterial blood pressure and heart rate, carotid occlusion, and nictitating membrane responses; however, such findings were still within the range obtained for these same variables from a group of control cats. No signs of toxicity or ECG changes were observed up to a cumulative IV dose of 18.7 mg/kg. In anesthetized dogs, no significant changes in the cardiovascular parameters were seen nor were there any effects on diuresis or ECG following an intra-arterial dose of 0.005 mg/kg or intraduodenal doses up to 5 mg/kg. A slight increase in heart rate was noted at the 5 mg/kg intraduodenal dose as compared with the controls.

5 Pharmacokinetics/ADME/Toxicokinetics

No PK/TK studies were conducted with naftifine HCl gel formulation.

6 General Toxicology

6.1 Single-Dose Toxicity

A number of acute toxicity studies have been conducted by the sponsor and reviewed by FDA. The following summary table was copied from the nonclinical review for IND

(b) (4) (dated 12/17/2004).

Study	Species	Dose	Route	Results
1. Acute oral toxicity on naftifine HCl, 1% cream (1984G)	Mice	20 ml/kg	Per os	Minimum lethal dose of naftifine hydrochloride 1% cream was found be greater than 20 ml/kg of body weight.
2. Acute toxicity by intravenous route on SN 105-843 (naftifine HCl), up to 0.415% soln. (1981H)	Mice	20 ml/kg	Intravenous	LD ₅₀ was found to be 65.2 mg/kg (60.2-70.6) in males and 67.6 mg/kg (61.2-77.0) in females.
3. Acute toxicity by intraperitoneal route on SN 105-843 (naftifine HCl), up to 4% emulsion (1980I)	Mice	20 ml/kg	Intra-peritoneal	LD ₅₀ was found to be 313 mg/kg (195-368) in males and 420 mg/kg (338-493) in females.
4. Acute oral toxicity on naftifine HCl, 1% cream (1984J)	Rats	20 ml/kg	Per os	Minimum lethal dose of naftifine hydrochloride 1% cream was greater than 20.0 ml/kg of body weight.
5. Acute oral LD50 toxicity on SN 105-843 (naftifine HCl) 3% solution (1981K)	Rats	8, 12, 16, 20, 24, 30 ml/kg	Per os	Predominant dose observations were: loss of righting reflex, ataxia, muscle flaccidity, docility & flattened body position. The calculated LD ₅₀ was 22.8 ml/kg.
6. Acute toxicity on SN 105-843 (naftifine HCl) 1% gel (1979A)	Mice	4000 mg/kg	Oral and subcutaneous	Mortality rates were too low to calculate LD ₅₀ . All surviving mice (37/40) were normal within 4-5 days. All rabbits were normal within 24 hours. Rats exhibited only irritation at injection site.
	Rats	4000 mg/kg 2000 mg/kg	Oral Subcutaneous	
	Rabbits	2000 mg/kg 1200 mg/kg 750 mg/kg	Oral Subcutaneous Dermal	
7. Acute dermal LD50 toxicity study on SN 105-843 (naftifine HCl) 3% solution (1981L)	Rabbits	2.0 ml/kg	Dermal	LD ₅₀ of SN 105-843 (naftifine HCl) is greater than 2.0 ml/kg. Mortality or signs of toxicity did not occur.

6.2 Repeat-Dose Toxicity

A number of repeat dose toxicity studies have been conducted with different formulations of naftifine HCl in rats, guinea pigs, rabbits, dogs, monkeys and minipigs. The summary information of these studies was cited from the nonclinical review for IND 77530 (dated 06/30/2008):

A 28-day subcutaneous toxicity study with naftifine HCl 1% gel (5, 15, and 45 mg/kg/day) was conducted in rabbits (1979). No deaths occurred. Decreased body weight associated with decreased food intake. Significant increase in basophiles at high dose was noted.

A 4-week dermal toxicity study with naftifine HCl 1% gel was conducted in dogs (1979). Only two doses (0, 500 mg/kg/day) were administered. Test article was well tolerated by the skin. No clinical, anatomical or histopathological changes were seen.

A 13-week oral toxicity study with naftifine HCl was conducted in rats (1978). Dose levels were 0, 25, 75, and 225 mg/kg/day. All low dose animals showed no noteworthy findings. In mid dose animals, a slight reduction in feed consumption and body weight gain was noted. A slight rise in serum bilirubin in males and females and liver weight increase in males was also observed. In high dose animals, reduced food consumption and body weight gain was noted. There were also moderate rise in serum bilirubin, increased serum urea in females and increased weight of liver and kidneys in both sexes. The biochemical and histological changes were not significant.

A 13-week oral toxicity study with naftifine HCl was conducted in dogs (1978). Dose levels were 0, 15, 45, and 135 mg/kg/day. A dose-dependent increase in frequency of emesis occurred during the first week. The NOAEL was identified as 135 mg/kg/day.

A 26-week dermal toxicity study with naftifine HCl 1% gel was conducted in rabbits (1980). Dose levels for the 1% gel were 0, 0.5, 1.5, and 2.25 g/kg/day (0, 5, 15, and 22.5 mg/kg/day for naftifine HCl) (The study description was cited from the summary table contained in the nonclinical review for IND 67823, dated 07/01/2004). The test article was very well tolerated in the study. Hematological, blood biochemical and urinary parameters remained within physiological limits. No anatomical or histopathological lesions were seen. The NOAEL was identified as 22.5 mg/kg/day.

A 26-week oral toxicity study with naftifine HCl was conducted in monkeys (1981). Dose levels were 0, 50, 100, and 200 mg/kg/day. The test article caused no significant changes. The NOAEL was identified as 200 mg/kg/day.

A one-month dermal toxicity study with naftifine cream was conducted in weanling minipigs (1992). Minipigs (4/sex/group) were treated with placebo cream, 1% naftifine cream (6 mg/kg/day), or 3% naftifine cream (18 mg/kg/day) twice per day for 30 days. Very slight erythema was observed in one placebo female (Days 2 and 3), one low dose female (Day 2), and two high dose females (Days 7 to 9). The erythema resolved within 1 or 2 days. This was not considered to be a significant treatment effect. At necropsy,

there were no treatment-related findings. Organ weights were similar in all the groups, and histopathology did not reveal any treatment-related changes. The NOAEL was identified as 18 mg/kg/day.

A six-month dermal toxicity study with 3% naftifine cream was conducted in rats (1984). SD rats (30/sex/group) were treated with vehicle cream (0.3 ml/day) or 3% naftifine cream (0.1 and 0.3 ml/day, 12 and 36 mg/kg/day). 77 rats (32% of all animals) from treated and control groups showed signs of sickness intermittently during the study. 35 rats (15%) died or were euthanized due to moribund conditions. The clinical signs and subsequent deaths were consistent with symptoms of murine respiratory mycoplasmosis and confirmed by blood test. There were no treatment-related effects on body weight, hematology, or clinical chemistry. The NOAEL was identified as 36 mg/kg/day.

A 28-week oral toxicity study was conducted with naftifine HCl in rats (1979). SD rats (15/sex/group) were treated via gavage at dose levels of 0, 25, 75, and 132/300 mg/kg/day. The high-dose animals were treated with 132 mg/kg/day from start to Day 26, 125 mg/kg/day on Days 27 to 32 (due to an error in test article preparation), and 300 mg/kg/day from Day 33 to the end of the study. 25 animals died during the study; most of these deaths were due to dosing errors or anesthetic shock during blood sampling. Signs of hypersalivation were observed in a few animals in the mid and high dose groups. A slight decrease in body weight (5% to 7%) was observed in mid dose and high dose males after 12 weeks of dosing, but no effect was noted in the females. In low dose animals, a rise in serum bilirubin in females at all test times and a rise in serum creatinine at the end of dosing were observed. In mid dose animals, a rise in serum bilirubin, serum creatinine, and blood urea, varying according to sex and sampling time, was noted. In high dose animals, a rise in serum bilirubin in males and a rise in serum creatinine and blood urea, varying according to sex and sampling time were observed. At necropsy, no gross changes were observed. Increased liver weight (both sexes) and kidney weight (males) were reported in the high dose animals after 28 weeks of treatment. By the end of the 4-week recovery period, these organ weights had returned to normal. The histopathological data were not complete; an assessment of potential treatment effects could not be made. The NOAEL was determined to be 25 mg/kg/day by Dr. Jiaqin Yao.

A 9-month dermal toxicity study with naftifine HCl solutions was conducted in minipigs (2004). Minipigs (6/sex/group) were treated topically with 0, 3%, 5%, or 10% naftifine HCl solutions. Dose levels were initially 0, 30, 50, and 100 mg/kg/day for Days 1-93, and were reduced to 0, 4.5, 7.5, and 15 mg/kg/day for the rest of study. Two animals died during the study due to chronic bronchopneumonia infection, which is not considered to be treatment-related. There were no significant changes in physical appearance or behavior. Dermal findings were mild with no clear indication of dose-related differences between the groups. Body weight growth was sustained in all the groups throughout the study. There were no significant effects on body weight in males. However, there was a clear trend of body weight decrease in the high dose females starting ~Day 99. Mean body weight in the high dose female group was approximately

12% less than that of the control group at the end of the study. There were no significant treatment-related histopathology findings. The NOAEL was identified by the sponsor as 15 mg/kg/d. Due to the significant body weight decrease noted in the high dose females, the NOAEL is identified as the mid dose, 7.5 mg/kg/day (5% solution).

7 Genetic Toxicology

The following genetic toxicology information for naftifine HCl is copied from the NAFTIN[®] Cream, 2% label.

“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).”

8 Carcinogenicity

To date there is no carcinogenicity data available for naftifine HCl. During the Pre-NDA meeting for IND 105603 (05/16/2012), the following comments were relayed to the sponsor:

“The Agency requests only one of the two products (NAFT-500 or NAFT-600) be tested for carcinogenicity to address the concern for carcinogenic potential of naftifine HCl. It is acceptable to conduct the 2-year dermal rat carcinogenicity study with the naftifine HCl cream formulation (i.e., NAFT-500).”

“We reiterate that a second carcinogenicity study may be needed, if the systemic exposure to the drug substance or its metabolites under maximal use conditions in humans is significantly high, or if data from the first carcinogenicity study indicate cause for concern (e.g., increased incidence of tumors or preneoplastic lesions).”

A 2-year dermal rat carcinogenicity study will be conducted as a PMR, which was stated in the approval letter for NDA 19599 S-11. The timetable for conduct of this study is:

Final Protocol Submission: 12/2012

Study Completion: 07/2015

Final Report Submission: 09/2016

Per the schedule the sponsor has submitted a carcinogenicity study protocol for review. The proposed doses received concurrence from the Executive CAC (meeting minutes dated 01/22/2013).

The Executive CAC recommendations and conclusions were:

- 1) *The Committee concurred with the sponsor’s proposed doses of 0 (untreated control), 0 (vehicle control), 1%, 2%, and 3% naftifine HCl cream applied to 10%*

- body surface area at 1 g/kg for both males and females (approximately 10, 20, and 30 mg/kg/day), based on MFD.
- 2) The Committee recommended that the test article remain on the animal treatment site for 24 hours/day instead of the proposed 6 hours/day. The Committee recommended that animals be caged individually at all times.
 - 3) It is noted that you have proposed to collect ~2.5 ml blood from 10/sex/group main study animals in Week 52 and at termination for the examination of clinical pathology, including hematology, coagulation, and clinical chemistry. The Committee recommended that the examination of clinical pathology be avoided in the mid-term (Week 52). It is noted that main study animals may not be bled during the study.
 - 4) The Committee noted that the sponsor should notify the Agency if there is excessive mortality and receive concurrence prior to changing dosing or terminating any dose group.

9 Reproductive and Developmental Toxicology

The following reproductive and developmental toxicology information is copied from the NAFTIN[®] Cream, 2% label.

“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 ((b)(4) X 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 ((b)(4) X 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 ((b)(4) X 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 ((b)(4) X MRHD). No developmental toxicity was noted at 100 mg/kg/day ((b)(4) X MRHD).

(b)(4)

Because the MRHD for NAFTIN[®] Gel, 2% would be half of the MRHD for NAFTIN[®] Cream, 2%, the multiples of human exposure for NAFTIN[®] Gel, 2% would be two times the corresponding multiples for NAFTIN[®] Cream, 2%.

10 Special Toxicology Studies

Naftifine HCl solutions 1%, 3%, 5%, and 10% were tested in a primary skin irritation study in rabbits (2003). 0.5 ml test article was applied to intact or abraded skin for an exposure duration of 24 hr. In the placebo and 1% groups, very slight erythema was observed on the abraded sites only of not more than 2 animals, which generally cleared within 24 hr. In the 3%, 5%, and 10% groups, very slight to well-defined erythema was observed in 1 to 3 animals which required up to 14 days to resolve in some cases. Out of a possible total index of 8.0, none of the primary irritation indices were higher than 1. The respective primary irritation indices for the intact and abraded sites were 0 and 0.17 (placebo), 0 and 0.08 (1%), 0.33 and 0.50 (3%), 0.17 and 0.75 (5%), and 0.50 and 0.67 (10%), respectively. Naftifine HCl solution was not considered a skin irritant in this study.

A dermal sensitization study in guinea pigs was conducted with naftifine HCl solution 5%, using a standard Buehler design (2003). The induction procedure was repeated three times a week for three consecutive weeks, with topical applications of 0.3 ml test article. Following a 2-week rest period, a challenge was performed on Day 33. 1-Chloro-2,4-dinitrobenzene (DNCB) was used as a positive control. Animals were examined for signs of erythema and edema for 14 days after challenge. No significant dermal reactions were noted. Naftifine HCl solution 5% was not considered a contact sensitizer in guinea pigs.

The drug product NAFT-600 gel, vehicle gel, the API naftifine HCl, and each of the excipients in the NAFT-600 gel formulation were tested for light absorbance with a UV/visible light scan (wavelength 280-700 nm). Both NAFT-600 gel and naftifine HCl exhibited minimal UVB absorbance (290 to 320 nm range) (Figures 1 and 2). There was little or no absorbance for the other ingredients. The extent of UVB absorbance does not trigger the need for a nonclinical phototoxicity study.

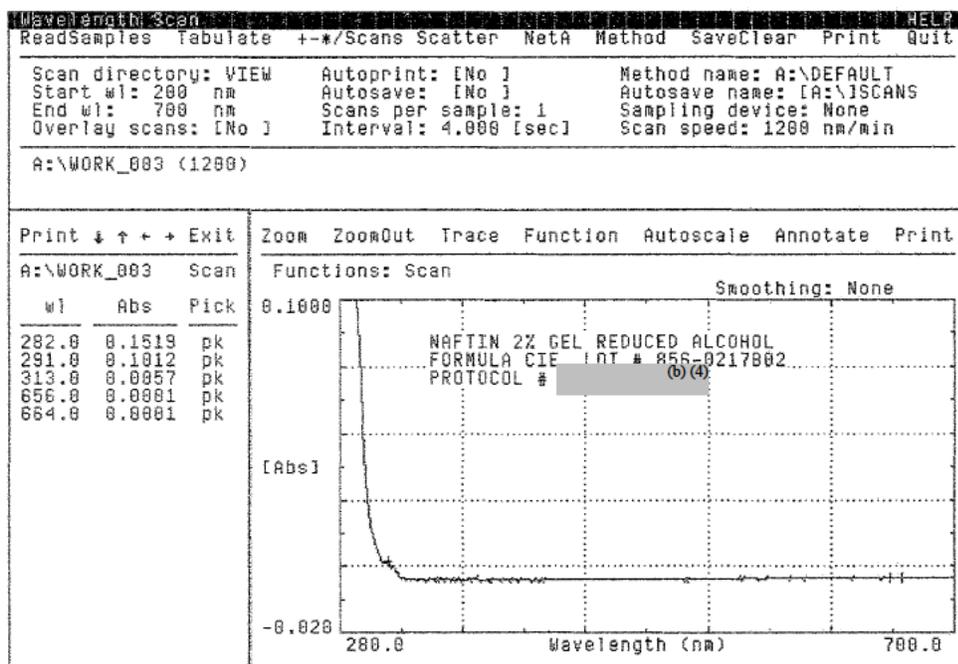


Figure 1. UV/visible light absorbance of NAFT-600 gel (solvent: methanol).

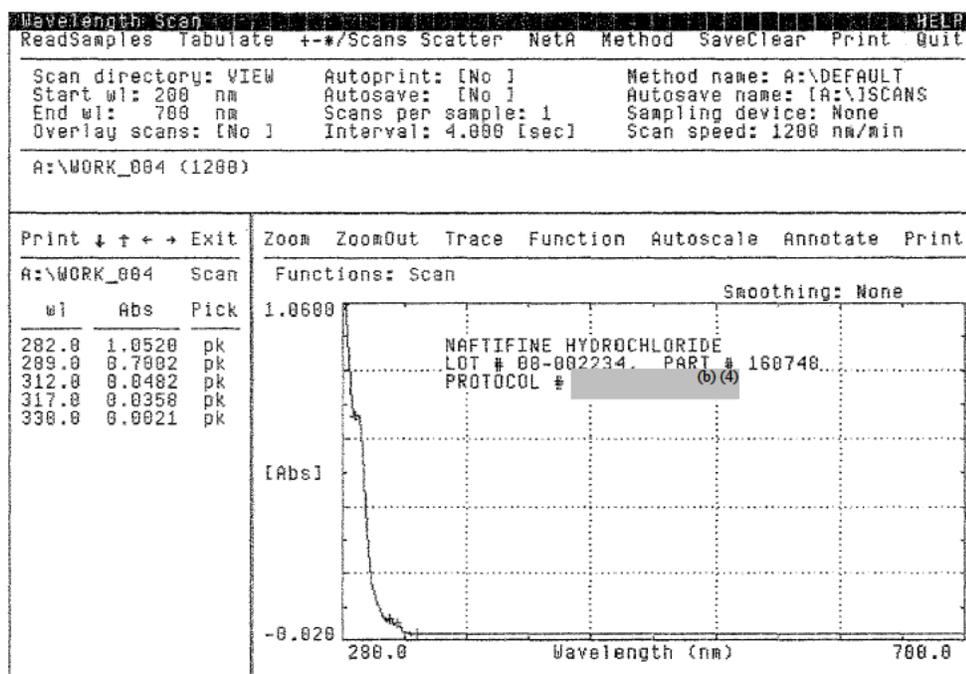


Figure 2. UV/visible light absorbance of naffine HCl (solvent: methanol).

A number of additional special toxicology studies were conducted with naffine HCl. The following summary table was copied from the nonclinical review for IND (b) (4) (dated 07/01/2004).

Study	Species	Dose	Route	Results
1. Primary skin irritation on SN 105-843 (Naftifine HCl) 3% solution (1980M)	Rabbits		Dermal	Skin irritation was determined by the Draize technique on intact and abraded rabbit skin. After 72 hours there was no skin irritation. SN 105-843 (naftifine HCl) was not considered a primary skin irritant.
2. Acute eye irritation study on naftifine HCl, 1% cream (1984Y)	Rabbits	0.1 ml	Eyes	Naftifine hydrochloride 1% cream was found to be slightly discomforting to the eye, slightly irritating to the conjunctiva, but not toxic to the cornea.
3. Acute eye irritation study on naftifine HCl, 3% cream (1984Z)	Rabbits	0.1 ml	Eyes	Naftifine hydrochloride 3% cream was found to be slightly discomforting to the eye, slightly irritating to the conjunctiva, but not toxic to the cornea.
4. Eye irritation study on SN 105-843 (naftifine HCl) 1% gel (1978AA)	Rabbits	0.1 ml	Eyes	No corneal or iris changes were observed. Conjunctival redness and edema were observed in 2 of the 6 animals. The irritant potential is limited to the conjunctiva. Therefore, instillation into the eye should be avoided
5. Eye irritation study on SN 105-843 (Naftifine HCl) 3% solution (1981BB)	Rabbits	0.1 ml	Eyes	SN 105-843 (naftifine HCl) 3% solution is considered an eye irritant. However, the solution contained 40% ethanol, and the irritation may be attributed to the alcohol.
6. An investigation of local sensitizing effect by intracutaneous administration of SN 105-843 (naftifine HCl), 1% solution (1979OC)	Guinea Pigs	1 st 0.05 ml, 2 nd -10 th 0.1 ml, challenge 0.05 ml	Intracutaneous	No skin reactions occurred during the injection series or with the challenge injection. No evidence of allergic reaction at the challenge injection site was seen upon histopathological examination
7. Cutaneous effects of naftifine cream 1% and vehicle (1979DD)	Rabbits	0.5 g	Cutaneous	Cream vehicle was non-irritating. Naftifine cream 1% was slightly irritating, but the faint lesions resolved in a few days.
8. Cutaneous tolerance of naftifine cream 1% and vehicle (1979EE)	Rabbits	0.5 g	Cutaneous	No mortality or abnormal weight development. No abnormalities seen in postmortem examination. Histological examination revealed thickening of epidermis on treated sites. Mild erythema and a few cases of slight edema reported.

11 Integrated Summary and Safety Evaluation

The proposed daily dosage of NAFTIN[®] Gel, 2% is comparable to the approved daily dosage of NAFTIN[®] Gel, 1% (once daily with 2% gel vs. twice daily with 1% gel). Because the proposed indication is limited to tinea pedis, the MRHD for NAFTIN[®] Gel, 2% (4 g/day, 1.33 mg/kg/day naftifine HCl) is half of the MRHD for NAFTIN[®] Cream, 2% (8 g/day, 2.67 mg/kg/day naftifine HCl).

With an intention to reduce irritation, the sponsor modified the formulation for NAFTIN[®] Gel, 2% (mainly lowered the concentration of alcohol), compared to NAFTIN[®] Gel, 1%. All excipients in the 2% gel formulation are below approved levels and there is no significant safety concern for the formulation change.

General toxicology studies have been conducted extensively with various formulations of naftifine HCl in rats, rabbits, guinea pigs, dogs, monkeys, and minipigs. Findings in oral toxicity studies included reduction in body weight gain and increases in serum bilirubin, creatinine, and urea levels. Findings in dermal toxicity studies included very slight erythema and reduction in body weight gain. Multiples of human exposure are calculated based on comparison with the identified NOAELs in pivotal toxicity studies (see the table below):

Study duration	Species	Route	NOAEL (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Multiples of human exposure*
13-week	Dog	Oral	135	73	55
28-week	Rat	Oral	25	4	3
26-week	Monkey	Oral	200	65	49
1-month	Minipig	Dermal (cream)	18	17	13
6-month	Rat	Dermal (cream)	36	5.8	4
26-week	Rabbit	Dermal (gel)	22.5	7.3	5
9-month	Minipig	Dermal (solution)	7.5	7.1	5

*Comparing to the human topical dose under maximum clinical use conditions: 1.33 mg/kg/day, assuming 100% absorption.

In genetic toxicology studies, naftifine HCl was negative in a bacterial mutagenicity test, an *in vitro* chromosome aberration test, and an *in vivo* micronucleus test. There is no concern for the genotoxicity of naftifine HCl. A 2-year dermal rat carcinogenicity study will be conducted as a PMR with naftifine HCl cream formulation.

Reproductive and developmental toxicology studies have been conducted with naftifine HCl in rats and rabbits. Oral administration of naftifine HCl to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 100 mg/kg/day. Oral doses of 30, 100 and 300 mg/kg/day naftifine HCl were administered during 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. Subcutaneous doses of 10 and 30 mg/kg/day naftifine HCl were administered during gestational days 6-15 to pregnant female rats. No treatment-related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day. Subcutaneous doses of 3, 10 and 30 mg/kg/day naftifine HCl were administered during gestational days 6-18 to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 30 mg/kg/day. A peri- and post-natal development study was conducted in rats. Oral doses of 30, 100 and 300 mg/kg/day naftifine HCl 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. No developmental toxicity was noted at 100

mg/kg/day. Multiples of human exposure are calculated based on comparison with the identified NOAELs in the reproductive and developmental toxicity studies:

Study	Species	Route	NOAEL (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Multiples of human exposure*
Fertility and general reproductive performance	Rats	Oral	100	16.2	12
Embryofetal study	Rats	Oral	300	48.6	37
Embryofetal study	Rats	Subcutaneous	30	4.9	4
Embryofetal study	Rabbits	Subcutaneous	30	9.7	7
Peri- and post-natal development study	Rats	Oral	100	16.2	12

*Comparing to the human topical dose under maximum clinical use conditions: 1.33 mg/kg/day, assuming 100% absorption.

Naftifine HCl solutions up to 10% were not irritating to rabbit skin. Naftifine HCl 5% solution was not a contact sensitizer in guinea pigs. Naftifine HCl and NAFT-600 gel exhibited minimal UVB absorbance. The extent of UVB absorbance does not trigger the need for a nonclinical photoirritation study.

Overall the toxicity profile of NAFTIN[®] Gel, 2% has been well characterized. Because TK data were not available for most toxicology studies, the multiples of human exposure were calculated based on BSA comparison, assuming 100% absorption after dermal application. It should be noted that the calculation of multiples of human exposure is very conservative when comparing NOAELs identified in systemic toxicology studies in which test article was administered via gavage or subcutaneous injection to topical clinical doses assuming 100% absorption. From a pharmacology/toxicology perspective, the proposed clinical dosage for NAFTIN[®] Gel, 2%, does not elicit a significant safety concern. This NDA is approvable from a pharmacology/toxicology perspective.

12 Appendix/Attachments

None.

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/s/

JIANYONG WANG
04/09/2013

BARBARA A HILL
04/09/2013

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 204286

Applicant: Merz Pharmaceuticals,
Greensboro, NC

Stamp Date:
08/31/2012

Drug Name: NAFT-600
(naftifine hydrochloride) Gel, 2%

NDA Type: Original-505(b)(1)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is an electronic CTD submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		The sponsor references nonclinical information contained in NDA 19599 to support this NDA. A dermal rat carcinogenicity study will be conducted as a PMR. The sponsor will submit the carcinogenicity study protocol by the end of 2012.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

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/s/

JIANYONG WANG
10/15/2012

BARBARA A HILL
10/15/2012