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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 21, 2013
From	David Kettl, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	204286
Applicant	Merz Pharmaceuticals, LLC
Date of Submission	August 31, 2012
PDUFA Goal Date	July 1, 2013
Proprietary Name / Established (USAN) names	Naftin (Naftifine) Gel 2%
Dosage forms / Strength	Topical Gel
Proposed Indication(s)	1. Interdigital tinea pedis (b) (4)
Recommended:	*Approval for Interdigital tinea pedis*

1. Introduction

The applicant, Merz Pharmaceuticals, submitted this application for a Naftin (naftifine) 2% Gel formulation for the indication of tinea pedis, and would provide for a shorter treatment duration compared to the currently marketed Naftin 1% Gel product. The proposed dosing regimen is once daily topical applications for 2 weeks.

Naftifine hydrochloride is the active ingredient of Naftin 1% Cream, approved in February 1988 under NDA 19599, and Naftin 1% Gel, approved in June 1990 under NDA 19356, for the treatment of tinea pedis, tinea cruris, and tinea corporis. Naftifine Cream, 2% was approved on January 13, 2012 for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organism *Trichophyton rubrum* in adults 18 years of age and over.

(b) (4)

The proposed product, naftifine gel 2%, is proposed for the treatment of tinea pedis (fungal infection of the foot and also known as "athlete's foot"). The applicant proposes that their application supports an indication of (b) (4) interdigital (b) (4) tinea pedis.

This NDA includes 2 Phase 3 safety and efficacy trials and 5 Phase 1 clinical trials, including a maximal use PK trial (MRZ 90200/1010/1) and a thorough QT trial (MRZ90200/1018/1).

The clinical review, by Dr. Milena Lolic, recommends an approval action for the treatment of the more limited indication of interdigital tinea pedis in adults, (b) (4) This application was reviewed by the Pediatric Review Committee (PERC), who concurred that additional clinical trial information across adolescence could be accomplished through a PREA post-marketing requirement that also addresses the needs for Naftin Cream 2%.

No new safety concerns were indentified in the trials conducted with naftifine gel 2%, though the product was noted to be more irritating than the currently approved formulations. Naftifine has a long history of marketed use, since 1988, and has not been associated with serious adverse events. There are no expected adverse events beyond the currently labeled local irritation, burning/stinging, dryness, itching, and erythema noted in the current prescribing information for the 1% gel and cream, and the 2% cream.

Outstanding issues from other review disciplines include the need for pharmacokinetic assessments in the adolescent population. The clinical pharmacology review by Dr. Doahn Tran concluded that there is insufficient PK information for the adolescent population, and recommends a post marketing requirement (PMR) for a pediatric (ages 12-17 years old).

This CDTL review concurs with the team's recommendation of approving naftifine gel 2% for the treatment of interdigital tinea pedis in adults, and concurs with the post marketing requirements discussed below.

2. Background

Naftifine hydrochloride is a synthetic allylamine derivative. The exact mechanism of antifungal action of naftifine is unknown, but investigations suggest the antifungal activity of naftifine hydrochloride is 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. The applicant has performed no new studies regarding the mechanism of action of naftifine.

When Naftin Cream 1% was developed in the 1980's, applicants were not required to separately assess the various clinical types of tinea pedis. Distinctions between interdigital and moccasin type tinea pedis were not generally made in clinical trials in that era. This applicant was advised of the need to specify definitive inclusion/exclusion criteria for different types of tinea pedis in their naftifine development programs as early as the preIND meeting for naftifine cream 2% on November 6, 2007, and included similar advice for this IND at the April

14, 2010 guidance meeting. The applicant was made aware that they should provide a pre-specified statistical analysis plan for the different tinea pedis types. The statistical analysis plan failed to adequately address this issue, and the recommended indication will be limited to interdigital tinea pedis.

3. CMC/Device

Naftin Gel 2% is a colorless to yellow gel containing naftifine hydrochloride (naftifine HCl) 2% as the active ingredient and the excipients (b) (4), propylene glycol, polysorbate 20, alcohol (b) (4) hydroxyethyl cellulose, benzyl alcohol, trolamine and edetate disodium.

The CMC review by Dr. Rajiv Agarwal concluded that this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product and has recommended of this application approval with an expiration dating period of 24 months.

The only review issue, acceptance criteria for degradation products, was amended as per Agency recommendations and was determined to be acceptable in April 2013.

The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application.

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%.

The drug product, a topical gel, is packaged in two different configurations, depending on whether it is the presentation for commercial distribution (45 g) or the physician samples (2 g).

Naftin Gel, 2% will be packaged in the 45g aluminum (b) (4) tubes, which is the same container closure systems (2 g and 45 g sizes) used to package the marketed Naftin Cream, 2% product (NDA 19599) approved in 2012.

There are no changes to the synthetic process since the approval of the previously approved naftifine NDA's. The information was deemed adequate by the CMC review. There are no outstanding product quality issues that would impact an approval action for this application.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was conducted by Dr. Jianyong Wang, who did not identify any approvability issues for this application.

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). No new requirements are recommended for this 2% gel formulation.

The sponsor references nonclinical information contained in NDA 19599 for Naftin Cream to support this NDA. There was no new nonclinical data submitted to this NDA.

From a pharmacology/toxicology perspective, the proposed clinical dose for Naftin Gel, 2%, does not cause significant safety concern. This application is approvable from a pharmacology/toxicology perspective, as the proposed clinical doses do not elicit any significant safety concerns. The applicant will complete a dermal rat carcinogenicity study as a post marketing requirement to the previously approved Naftin Cream 2% application.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was authored by Dr. Doahn Tran. He identified no issues that would adversely impact an approval action for this application. However, his review concurs with the team recommendation that the indication be limited to adults and the applicant should be required to conduct a PK/safety/tolerability trial as a PMR.

Systemic bioavailability of naftifine hydrochloride or its metabolites is not necessary for therapeutic effect against dermatophytes, as the topical products are thought to act locally against specific fungal organisms.

Dr. Tran summarized the pertinent clinical pharmacology issues as follows.

The sponsor conducted a maximal use pharmacokinetic (PK) trial in 32 adult male and female subjects with tinea pedis. This study administered a mean of 3.9 grams naftifine gel, 2% to both feet once daily for 2 weeks. All 32 enrolled subjects had tinea pedis on both feet and the majority of subjects (97%) had both interdigital and moccasin-type infections. Thirty subjects completed the trial.

Plasma naftifine concentrations were measurable in all 30 subjects. Plasma naftifine exposure increased 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. 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 generally increased during the trial period and reached steady state after 11 days. The fraction of dose excreted in urine was ≤ 0.01% of the applied dose.

Based on a cross study comparison, the systemic naftifine exposure (both AUC and Cmax) following application of naftifine gel, 2% to subjects with tinea pedis were about 3 fold lower than those seen for Naftin Cream, 2% applied to subjects with both tinea pedis and tinea cruris.

The pharmacodynamics of naftifine hydrochloride has not been established.

An oral dose of naftifine was used in the QT trial. Since the systemic exposure following naftifine gel, 2% application is much less than the exposure following an oral dose of 600 mg used in the thorough QT trial and the fact that there was no significant QTc prolongation with 600 mg oral dose, it can be concluded that there is no concern regarding QTc prolongation with naftifine gel, 2% for treatment of tinea pedis

According to the IRT-QT team overall summary of findings: "No significant QTc prolongation effect of naftifine HCl (600 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between naftifine HCl (600 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines."

From a clinical pharmacology perspective, this application is acceptable pending agreements on the recommended labeling changes, the Post Marketing Requirement (PMR) for a

pediatric/adolescent (ages 12-17 years old) safety/pharmacokinetic (PK) study in subjects with tinea pedis.

6. Clinical Microbiology

The clinical microbiology review by Dr. Simone Shurland concludes that the application is acceptable from a clinical microbiology perspective. Her conclusion states:

"From a clinical microbiology perspective the information provided by the Applicant supports the efficacy of NAFT-600 Gel 2% for the treatment of interdigital type (b) (4) *tinea pedis. NAFT-600 Gel 2% was shown to be active against T. rubrum, T. mentagrophytes and E. floccosum.*

There are only minor wording changes to the Applicant's proposed package insert microbiology subsection."

The applicant has provided information sufficient to allow all three of the most common causative organisms in labeling. This was not the case in the application for Naftin Cream, 2%, which only had adequate information related to the effects of *T. rubrum. T. mentagrophytes* and *E. floccosum* were not allowed in the Naftin Cream 2% labeling.

The 1% naftifine gel and cream formulations were approved for the treatment of *Trichophyton rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum*. In addition, the 1% gel formulation was approved for the treatment of *Trichophyton tonsurans*.

She also notes in her review that "To date, a mechanism of resistance to naftifine has not been described. In a multiple passage study, no increase in MICs was observed in isolates exposed to multiple concentrations of naftifine."

There are no outstanding issues related to clinical microbiology other than conclusion of labeling negotiations.

7. Clinical/Statistical- Efficacy

The applicant conducted two Phase 3 safety and efficacy trials and 5 Phase 1 clinical trials, including a maximal use PK trial, a thorough QT trial, and provocative dermal safety studies to support the safety and efficacy of Naftin Gel 2% for the indication of tinea pedis.

The applicant's objective was to support an efficacy claim of "interdigital (b) (4) tinea pedis". Although the efficacy for the treatment of interdigital tinea pedis is supported by Agency analysis, (b) (4)

The Biostatistical review, by Dr. Carin Kim, concludes that "the endpoints related to the (b) (4) were 'other secondary endpoints', the protocol did not include methods to adjust the multiplicity to control the Type I error rate for these endpoints, and furthermore, not all subjects with (b) (4) assessed at baseline for positive KOH and positive culture at baseline. Because the studies were not conducted to evaluate the (b) (4) for establishing an efficacy claim, the results of (b) (4) should be considered to be exploratory at best."

The Agency provided consistent advice since at least 2007 in meetings with this applicant for both the Naftin Gel and Cream development programs related to the need to distinctly assess interdigital (b) (4) in inclusion/exclusion criteria and in statistical analyses. Specifically, the phase 3 protocols were reviewed in early 2011 and the Agency stated that details of the sensitivity and supportive analyses should be prespecified in the protocol rather than deferred to the statistical analysis plan. The Agency also stated that the proposed primary imputation method was not clear. Despite this advice, and the approval of Naftin Cream 2% in January, 2012 for only interdigital tinea pedis, (b) (4)

The primary endpoint of interdigital tinea pedis was successful in two adequate and well controlled trials. The protocol-specified primary efficacy endpoint was the proportion of subjects with complete cure of interdigital tinea pedis at Week 6 where complete cure is defined as negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus (grade 0 for each) evaluated using a 4-point severity grade (0=absent, 1=mild, 2=moderate, 3=marked).

The applicant's analysis from Dr. Kim's review is below:

Applicant's Analysis for Interdigital Type Tinea Pedis (Primary and Key Secondary efficacy endpoints)

		NAFT-600	Vehicle	p-value[4]
Study MRZ 3015		382	179	
Interdigital	Complete Cure [1]	64 (16.8%)	3 (1.7%)	<0.001
	Effective Treatment [2]	207 (54.2%)	11 (6.1%)	<0.001
	Mycological Cure[3]	250 (65.4%)	25 (14.0%)	<0.001
Study MRZ 3016		400	213	
Interdigital	Complete Cure[1]	104 (26.0%)	7 (3.3%)	<0.001
	Effective Treatment[2]	203 (50.8%)	15 (7.0%)	<0.001
	Mycological Cure [3]	235 (58.8%)	22 (10.3%)	<0.001

Source: Applicant's Analysis.
(1) Complete Cure is defined as having negative mycology results (dermatophyte culture and KOH) and absence of erythema, scaling and pruritus at Week 6.

(2) Effective Treatment is having negative KOH, negative culture, and scaling, erythema, and pruritus grade of 0 or 1
(3) Mycological cure is having negative KOH and negative culture.
(4) P-values are calculated from a one-sided CMH test stratified by pooled sites (FAS, MVTF).

Approximately 11% and 8% of the subjects discontinued Study MRZ 3015 and Study MRZ 3016, respectively, before Week 6. The most common reason for discontinuation was "lost to follow-up." Subject demographics were comparable across the study groups. All study sites were in the United States and Puerto Rico.

Efficacy results appear to be relatively consistent across the pooled study sites in the Agency analysis. There did not appear to be impacts on the efficacy results based on gender or age. Subjects ≥ 65 years of age showed higher cure rates (23/63; 37% active v. 1/40; 2% for vehicle) then the rest of population. There are issues related to sample size in terms of drawing any conclusions for labeling.

Both the clinical and biostatistical reviews conclude that approval is warranted for interdigital tinea pedis in adults. This CDTL review concurs with this recommendation, and draft labeling will be communicated to the applicant with this indication.

8. Safety

Naftifine cream has been approved at the 1% concentration since 1988 for the 1% cream, and since 1990 for the 1% gel, and risks associated with naftifine use have been low.

The data base for safety evaluation of Naftin Gel 2% is comprised of 1747 subjects (1144 randomized to NAFT-600 and 571 subjects randomized to vehicle in two phase 3 trials, plus 32 subjects from an open label, uncontrolled PK trial).

There were no deaths reported in any trial in the development program.

Serious adverse events (SAEs) were reported by 9 subjects (5 exposed to Naftin Gel) and did not appear to the applicant or the clinical review team to be related to the study drug. One subject was coded for two "severe" events, but on review, these both appeared to be based on subject assessment only, and seemed related to progression of disease, not as a drug effect. These were deemed by the team to be unwarranted for labeling.

Approximately 20% of subjects treated with NAFT-600 reported adverse events (AE), most of which had similar rates when compared to vehicle and did not appear to be related to the drug.

Application site reactions were reported by 2% of subjects in the Naftin Gel arms and 1% in vehicle arms. These data should be included in labeling as they are supported by dermal safety studies which showed that Naftin Gel 2% has the potential to cause application site irritation.

Application site adverse events (AE) for the general disorders and administration site conditions are summarized below in the table from Dr. Kim's review.

Number (%) of subjects with treatment-emergent adverse events

Application site AE	Study MRZ 3015		Study MRZ 3016	
	NAFT-600 N=571(1)	Vehicle N=284(1)	NAFT-600 N=572(1)	Vehicle N=287(1)
Pain	3 (0.5%)	1 (0.4%)	2 (0.3%)	1 (0.3%)
Edema Peripheral	1 (0.2%)	-	1 (0.2%)	-
Dermatitis	1 (0.2%)	-	-	-
Dryness	1 (0.2%)	1 (0.4%)	-	-
Erosion	1 (0.2%)	-	-	-
Fissure	1 (0.2%)	-	-	-
Paraesthesia	1 (0.2%)		1 (0.2%)	-
Swelling	1 (0.2%)	-	-	
Pruritus	-		1 (0.2%)	-
Vessel puncture site pain	1 (0.2%)	-	-	-
Exfoliation	-	-	1 (0.2%)	1 (0.3%)
Rash	-	-	1 (0.2%)	-

Source: Applicant's tables 54 and 58, study report
(1) Safety evaluation set (SES).

The adverse event profile was largely consistent with what is known about topical naftifine hydrochloride from previous clinical trials and from the post-approval use of approved naftifine products. The new safety information for this 2% formulation is the potential of Naftin 2% Gel to cause irritancy and labeling is adequate to characterize this adverse event.

There were no clinically meaningful trends observed for any of the laboratory parameters. Electrocardiograms were not obtained during Naftin Gel 2% clinical trials.

Provocative dermal safety study results demonstrated application site irritation, and little risk as a primary sensitizer.

A long term safety study is deemed unnecessary for this application. Given the fact that the currently approved labeling for Naftin Gel 1% specifies dosage and administration instructions that are not specific amounts ("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 the evening"), this CDTL review concludes that adequate information is available based on the long term historical use of Naftin Cream and Gel 1% since 1988. A long term safety study would not be particularly useful for labeling, in that patients will self limit application amounts in the face of local irritative side effects, and that no significant pattern of adverse events have been reported over two decades of use for the 1% cream and gel formulations.

9. Advisory Committee Meeting

No Advisory Committee meetings were required, nor held for this application.

10. Pediatrics

The applicant is seeking a waiver of pediatric studies in pediatrics less than 12 years of age and deferral of pediatric studies in age range of 12-17 years to be conducted post approval.

The pathophysiology and causative organisms for tinea pedis is similar in adolescents to adults. It does not seem necessary to demand efficacy data for the adolescent population, and efficacy can be reasonably extrapolated to adolescents. The applicant's rationale that tinea pedis is uncommon in pre-pubertal patients is reasonable, and a waiver for the population under 12 years of age is acceptable.

There were 3 subjects under age 18 in one phase 3 trial and 7 subjects in the second phase 3 trial. It is the recommendation of the review team that additional safety data should be required for an age indication of 12 years of age and older.

The application does not contain any PK data for Naftin Gel 2% in pediatric subjects. However, the proposed indication is for treatment of patients (b) (4) years of age and older. Due to the lack of systemic bioavailability data and limited clinical experience with naftifine gel, 2% in pediatric subjects during product development, it is recommended that the indication be limited to adults and a PMR to conduct a PK/safety/tolerability trial in adolescents is recommended.

The applicant has proposed to include a Naftin Gel 2% arm in the planned protocol to address the PMR for Naftin Cream 2%. The PeRC generally concurred with the proposal to address the safety and pK informational needs in the same study to address the PMR from the January 2012 approval for Naftin Cream.

In the interim, it is recommended that a PMR be included in the approval letter to conduct pharmacokinetic/Safety/Tolerability trial under maximal use conditions in adolescent subjects ages 12 years to 17 years 11 months with a minimum of at least 18 evaluable subjects with tinea pedis interdigital-type.

11. Other Relevant Regulatory Issues

Two study sites were selected for DSI inspection due to the relatively high treatment responders and large numbers of subjects enrolled (Rochester, NY and Melbourne, FL).

According to the DSI review finalized March 5, 2013, no violations were noted. The clinical trials appear to have been conducted adequately, and the data generated appear acceptable in support of the application.

There were no issues identified with financial disclosures or GCP guidelines.

12. Labeling

Review of the proposed label submitted by the applicant was based on evaluation of the clinical trials for the NDA as well as DMEPA, DRISK, and DDMAC consultative reviews.

Labeling is adequate to communicate necessary safety information to prescribers. Labeling generally follows the precedent label of Naftin Cream 2% which was approved in January, 2013.

As noted above, the applicant will be presented with prescribing information that differs from their proposal in terms of the more limited indication of interdigital tinea pedis as well as limitation of the population to adults.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The clinical team leader concurs with the primary clinical reviewer, and that of the review team, that this product should be approved for the indication of interdigital tinea pedis, in adults, pending successful completion of labeling negotiations with the applicant.

- Risk Benefit Assessment

Efficacy for interdigital tinea pedis has been adequately demonstrated in two adequate and controlled trials. (b) (4)

The safety findings are largely limited to local adverse events, with no serious adverse events deemed related to the study product. The local adverse events are expected given the marketing experience of 1% Naftin products since 1988, and are not dissimilar in scope and severity.

The benefits of this product outweigh the risks when used as the prescribing information recommends for adults, and this CDTL review concurs that this application should be approved for patients > 17 years of age. The conclusion that this application should be approved is shared by each review discipline, and there are no outstanding approvability issues beyond agreement on final product labeling.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

REMS is neither required nor recommended for this topical antifungal product. Labeling is adequate to inform prescribers and patients of expected adverse events and risks.

- Recommendation for other Postmarketing Requirements and Commitments

The rationale for the recommended PMR is described above. Discussions with the applicant for proposed labeling now in process. The applicant has already agreed to the two year carcinogenicity study as a post-marketing requirement under the Naftin Cream 2% approval action from January, 2012.

The PMR should state:

Conduct a Pharmacokinetic/Safety/Tolerability trial under maximal use conditions in subjects ages 12 years to 17 years 11 months with a minimum of at least 18 evaluable subjects with tinea pedis towards the upper end of disease severity in the patient population.

- Recommended Comments to Applicant

There are no other recommended comments exclusive of agreed upon labeling in PLR format. Labeling discussions have not been initiated with the sponsor as of the date of this review. The post marketing commitments/requirement is discussed above and also requires agreement by the applicant as labeling discussions proceed.

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/s/

DAVID L KETTL
06/04/2013