CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204286Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 25th, 2013
From	Susan J. Walker, MD, FAAD
Subject	Division Director Review
NDA #	204286
Applicant Name	Merz Pharmaceuticals, LLC
Date of Submission	August 31st, 2012
PDUFA Goal Date	July 1st, 2013
Proprietary Name / Established (USAN) Name	Naftin/Naftifine
Dosage Forms / Strength	Topical Gel/2%
Proposed Indication(s)	1. Interdigital tinea pedis (b) (4)
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Milena Lolic/David Kettl
Statistical Review	Carin Kim/Mohamed Alosh
Pharmacology Toxicology Review	Jianyong Wang/Barbara Hill
CMC Review	Rajiv Agarwal/Shulin Ding
Microbiology Review	Simone Shurland/Lynette Berkeley
Clinical Pharmacology Review	Doan Tran
CDTL	David Kettl

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This application is a standard submission for approval of a topical antifungal drug product for the treatment of tinea pedis. The active moiety, naftifine hydrochloride, is currently approved in other topical dosage forms and strengths for the treatment of tinea pedis. The review team is in agreement regarding the approvability of the submission. This review will summarize the review team findings as described primarily in the cross discipline team leader review by Dr. Kettl.

2. Background

Naftifine hydrochloride is the active ingredient in 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 in January 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.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of (b) (4) months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer, Dr. Wang, that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

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 was 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.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer, Dr. Tran, that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the sections of the clinical microbiology review regarding the microbiology section of the label (12.4). The drug product has been shown to be active against most isolates of the following fungi, both *in vitro* and in clinical infections:

Trichophyton rubrum
Trichophyton mentagrophytes
Epidermophyton floccosum

I concur with the conclusions reached by the clinical microbiology reviewer, Dr. Shurland, that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Tinea pedis includes several subtypes, the most common being interdigital and moccasin. As detailed in "Dermatology", (2nd Edition, Bolognia et al) the interdigital type is the most common, and is characterized by erythema, scaling, maceration and fissures occurring between the toes. Moccasin type features a diffuse hyperkeratosis, erythema and scaling on one or both of the plantar surfaces, is frequently chronic, and more difficult to cure.

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.

Two adequate and well controlled trials demonstrated that naftifine 2% gel was successful in the treatment of interdigital tinea pedis. The protocol-specified primary efficacy endpoint was the proportion of subjects with complete cure of interdigital tinea pedis at Week 6. Complete cure was defined as negative mycology results (dermatophyte culture and KOH) and absence of clinical signs and symptoms (erythema, scaling and pruritus).

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)

	Trial 1		Trial 2	
Endpoint	NAFTIN Gel, 2% N=382 n (%)	Vehicle N=179 n (%)	NAFTIN Gel, 2% N=400 n (%)	Vehicle N=213 n (%)
Complete Cure[a]	64 (17%)	3 (2%)	104 (26%)	7 (3%)
Treatment Effectiveness[b]	207 (54%)	11 (6%)	203 (51%)	15 (7%)
Mycological Cure[c]	250 (65%)	25 (14%)	235 (59%)	22 (10%)

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

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. Both the clinical and biostatistical reviews conclude that approval is warranted for interdigital tinea pedis in adults, and I concur with this recommendation and the recommendations for product labeling.

8. Safety

1144 patients were exposed to NAFT-600 (naftifine 2% gel) in phase 3 trials. Application site reactions were reported by 2% of subjects receiving naftifine 2% cream and 1% of subjects in the vehicle arm. The adverse event profile is consistent with other topical antifungals and raises no safety concerns. There were no deaths reported in any trial in the development program.

Naftifine topical formulations with postmarketing safety information include naftifine cream 1% (since 1988), naftifine gel 1% (since 1990) and naftifine cream 2% (since 2012). There are no safety concerns/signals for the naftifine topical moiety.

9. Advisory Committee Meeting

No advisory committee meetings were required, nor held, for this application.

10. Pediatrics

We concur with the applicant's waiver request for pediatric study requirements for ages 0-11 because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. Tinea pedis is not prevalent in the population younger than 12 years of age and the Division concludes that studies are highly impracticable.

We are deferring submission of pediatric studies in the age range of 12-17 years, because this product is ready for approval for use in adults and the necessary pediatric studies have not been completed. The applicant will conduct a pharmacokinetic/safety/tolerability trial under maximal use conditions in adolescent subjects ages 12-17 yr. 11 months with a minimum of 18 evaluable subjects with tinea pedis interdigital type.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

12. Labeling

- Physician and carton/container labeling have been agreed upon with the applicant. There are no outstanding issues that preclude an "approval" action.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – This application will be approved for the treatment of interdigital tinea pedis

- Risk Benefit Assessment – The benefits of this product outweigh the risks when used as described in labeling for the treatment of interdigital tinea pedis. The review team is aligned on the recommendation for approval, and there are no outstanding unresolved issues.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – A postmarketing REMS is neither required nor recommended for this product.

- Recommendation for other Postmarketing Requirements and Commitments – The applicant has agreed to the following post-marketing requirement:

    - To 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 interdigital type.

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/s/

SUSAN J WALKER
06/27/2013