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RESEARCH**

APPLICATION NUMBER:

204427Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 8, 2014
From	David L. Kettl, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 204 427 Related IND: 71206
Supplement#	
Applicant	Anacor Pharmaceuticals, Inc.
Date of Submission	July 29, 2013
PDUFA Goal Date	July 29, 2014
Proprietary Name/ Established (USAN) names	Kerydin (tavaborole) topical solution 5%
Dosage forms / Strength	Topical solution
Proposed Indication(s)	Treatment of onychomycosis of the toenail
Recommended:	<i>Approval</i>

1. Introduction

This 505 (b)(1) application for a new molecular entity, tavaborole, is submitted by Anacor Pharmaceuticals, Inc., and is reviewed under the PDUFA V Program for NME NDA's. Tavaborole is an oxaborole, and is the first of a new class of antifungal products. The mechanism of action of tavaborole is inhibition of fungal protein synthesis. The formulation is a solution for topical application to the toenail. There have been no approvals of a topically applied product for onychomycosis since 1999--- Penlac (ciclopirox). Kerydin has been accepted as the trade name for this new drug product.

The applicant proposed an indication of "for the treatment of onychomycosis (b) (4) (b) (4) the submitted data support (b) (4) indication of "toenail onychomycosis caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*."

Efficacy was demonstrated in two successful phase 3 trials and adverse reactions were infrequent. Most of these adverse reactions were limited to application site reactions and resolved without treatment. The review team identified no systemic safety concerns.

As the clinical team leader and CDTL for this application, I concur with the recommendation of Dr. Milena Lolic, the primary clinical reviewer, that this application should be approved as an adequate risk benefit determination has been demonstrated by the applicant.

There are no outstanding issues from the CMC, Pharmacology/Toxicology and Biostatistics review teams that would impact approval of this application.

2. Background

Tavaborole is a novel (b) (4) boronic acid complex that exhibits broad-spectrum antifungal activity against dermatophytes, yeasts, molds, and other filamentous fungi. It is the first in a new class of oxaborole antifungal agents. It has not been approved in any jurisdiction.

The IND for tavaborole was opened in 2005 with a pharmacokinetics study. The Agency had multiple interactions with the applicant to discuss the development program and included notable landmark meetings:

- Pre-IND meeting (10/3/2005)
- Guidance meeting (6/11/2007)
- Guidance meeting (8/13/2008)
- End of Phase 2 meeting (10/28/2009)
- Guidance meeting (11/14/2012)
- Pre-NDA meeting (5/29/2013)

In addition, a Special Protocol Assessment was conducted, and the applicant received a SPA agreement letter on September 13, 2010. The clinical review notes that the content of this NDA is consistent with the prior agreements with the Division.

Onychomycosis is a chronic fungal infection of toenails and/or fingernails. The clinical manifestations of onychomycosis include separation of the nail plate from the nail bed (onycholysis), subungual hyperkeratosis, and changes in the nail plate that make it thicker, brittle, and discolored. The most common site of infection is the toenail.

The most common fungal organisms which cause toenail onychomycosis are *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. Fingernail onychomycosis is more likely to be caused by yeasts, most commonly *Candida albicans*. In the course of development, only toenail onychomycosis subjects were included in clinical trials, (b) (4)

Hence, the review team does not concur with the (b) (4) (b) (4).
The applicant proposed an indication of “for the treatment of onychomycosis (b) (4) (b) (4) but the review team recommends (b) (4) of “toenail onychomycosis caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.”

3. CMC/Device

Kerydin Solution, (tavaborole) 5% is an alcohol/propylene glycol based clear, colorless solution containing 5% tavaborole (w/w). In addition to the active ingredient, the drug product

contains Alcohol USP, Propylene Glycol USP and Edetate Calcium Disodium USP. The levels of usage of each inactive ingredient in the final drug product are below those listed in the IIG for the same route of administration.

(b) (4)

The CMC review by Dr. Gene Holbert notes that the proposed drug product specification includes tests and acceptance criteria for the following attributes: description, identity, tavorole assay, impurities, EDTA assay, packaging integrity, weight loss, minimum fill, and microbiological testing. The CMC review concludes that the proposed specification is supported by data and is acceptable.

The to-be-marketed formulation is the same as that used in Phase 3 clinical trials and registration stability batches. Stability data indicate that the drug product is physically and chemically stable with no significant changes observed when stored at 25° C for up to 24 months.

The primary container closure system for tavorole topical solution, 5% is a 12-mL amber USP (b) (4) glass bottle with an 18-400 neck finish and an 18-400 black (b) (4) closure with (b) (4) liner. Upon first use, the patient is instructed to replace the primary closure ((b) (4) closure) with the dropper assembly provided in the carton. Each milliliter of solution contains 43.5 mg of tavorole (the density of the drug product solution is (b) (4)).

The microbiological examination procedures in conjunction with method validation were reviewed and found adequate by the Agency microbiologist, Erika Pfeiler, Ph.D. Microbial limits testing for product release and stability was waived as the product is inherently antimicrobial and the applicant has performed suitable microbiological testing during development.

The conclusion from the ONDQA review team is that the applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. There are no outstanding CMC issues beyond completion of labeling negotiations with the applicant.

The Office of Compliance has issued an overall “Acceptable” recommendation for the facilities involved in the NDA.

4. Nonclinical Pharmacology/Toxicology

The nonclinical program for this new molecular entity was reviewed by Dr. Barbara Hill. She provides the following summary of the pertinent nonclinical findings.

Repeat dose oral toxicity studies up to 6 months in rats have been conducted with tavorole and repeat dose dermal toxicity studies up to 9 months in minipigs have been conducted with tavorole solution. The target organ of toxicity identified in oral rat toxicity studies was the nonglandular stomach which exhibited as epithelial hyperplasia and hyperkeratosis. The nonglandular stomach is absent in humans. Therefore, the clinical significance of this finding is unclear.

The target organ of toxicity identified in the dermal minipig toxicity studies was the skin at the site of application which exhibited a dose dependent increase in the incidence and severity of dermal irritation. Both the treatment related effects on the nonglandular stomach in rats and at the treatment site in minipigs were reversible after stopping treatment.

Tavorole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

An oral carcinogenicity study in rats was conducted with tavorole and a dermal carcinogenicity study in mice was conducted with tavorole solution. No drug related increase in the incidence of neoplasms was noted in either carcinogenicity study.

The potential reproductive toxicity of tavorole was evaluated in an oral fertility study in rats, oral embryofetal development studies in rats and rabbits, a dermal embryofetal development study in rabbits and an oral pre- and post-natal development study in rats. No treatment related effects on fertility were noted in rats at oral doses up to 300 mg/kg/day tavorole. In the oral embryofetal development study in rats, a treatment related increase in embryofetal resorption and/or embryofetal death was noted at an oral dose of 300 mg/kg/day tavorole which correlated with maternal toxicity (significant body weight decrease). Drug related skeletal malformations and variations suggestive of delayed development were noted in fetuses at the 300 mg/kg/day tavorole dose in rats.

The NOAEL for drug related malformations was 150 mg/kg/day. The NOAEL for maternal toxicity and embryofetal toxicity was 50 mg/kg/day.

Tavorole solution was slightly irritating to intact rabbit skin after a single 24 hour topical application under occlusion and was an ocular irritant in rabbits. Tavorole solution was classified as a non-sensitizer in guinea pigs. The need for a nonclinical photoirritation study was waived for tavorole solution since no absorption was noted from 225 nm – 700 nm.

Dr. Hill's review concludes that the toxicity profile of tavorole solution has been well characterized by the nonclinical studies conducted by the applicant, and concluded that there is no significant safety concern for tavorole solution at the proposed clinical dose. There are no outstanding nonclinical issues for this application beyond agreement on labeling.

Dr. Hill recommended approval for this application from a pharmacological/toxicological perspective and recommended no nonclinical post marketing requirements.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology review was conducted by Dr. An-Chi Lu. Tavaborole was found to undergo extensive metabolism and renal excretion is the major source of elimination from the body.

Dr. Lu reviewed a maximal use PK trial to determine the PK of tavaborole 5% solution in subjects with toenail onychomycosis following topical administration. A total of 24 subjects diagnosed with distal subungual onychomycosis involving at least 4 toenails, including at least one great toenail were treated with a single dose of tavaborole 5% solution (approximately 200 μ L) on all 10 toenails, including up to 2 mm of the surrounding skin on Day 1. All subjects received once daily dosing for 14 consecutive days on Days 5 to 18.

After a single topical application on Day 1, the mean C_{max} (\pm standard deviation) in plasma was 3.54 ± 2.26 ng/mL, the mean AUC_{last} was 44.4 ± 25.5 ng*hr/mL, and the median T_{max} was 12 hours (range 4.03-23.9 hours). After 14 days of repeated daily applications, the mean C_{max} was 5.17 ± 3.47 ng/mL, the mean AUC_{τ} was 75.8 ± 44.5 ng*hr/mL, and the median T_{max} was 8.03 hours (range 0.47-24.0 hours). Both the mean C_{max} and AUC increased from Day 1 to Day 18, with values of C_{max} increased from 3.54 ng/mL to 5.17 ng/mL and AUC from 44.4 ng*hr/mL to 75.8 ng*hr/mL. The accumulation ratio based on AUC was 2.2.

Based on the plasma trough concentrations, steady state was reached on Day 11 after 6 days of daily dosing.

From the review of Interdisciplinary Review Team for QT Studies Consultation, Dr. Moh Jee Ng concluded that no significant QTc prolongation effects of tavaborole (doses of topical solution, 5% q.d. and topical solution, 5% b.i.d.) were detected.

The drug-drug interaction potential of tavaborole was assessed in the in vitro inhibition and induction studies. The results indicated that tavaborole is not likely to induce the activity of CYP isoenzymes. Dr. Lu recommends the following for section 7.0 of product labeling:

“No formal drug-drug interactions studies have been conducted with tavaborole. In vitro studies have shown that tavaborole, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.”

The applicant did not provide any PK data for tavaborole topical solution, 5% in pediatric subjects. A PMR for a pharmacokinetic/safety trial in 40 pediatric subjects age 12-17 years and 11 months with onychomycosis of toenails [REDACTED] ^{(b) (4)} was recommended by

the review team and was acceptable to the applicant. This trial will include assessment of PK under maximal use conditions in a subgroup of at least 16 evaluable subjects.

[REDACTED] (b) (4)

The conclusion of Dr. Lu's review is that the application is acceptable from a Clinical Pharmacology perspective pending agreement on recommended labeling changes. The recommended PMR which will include adolescent pK assessments has been accepted by the applicant.

6. Clinical Microbiology

The clinical microbiology review was conducted by Dr. Kerian Grande Roche. Mycological testing (fungal culture and KOH wet mount) was performed in five Phase 2 studies and in two Phase 3 studies of subjects with onychomycosis. The central review issue was the proposed indication, "for the treatment of patients with onychomycosis [REDACTED] (b) (4)," and whether adequate information was presented to support such an indication.

Microbiologic studies were completed to determine mechanism of action, mechanism of resistance, spectrum of antimicrobial activity of tavaborole, and comparison to commercially available antifungals approved for the treatment of onychomycosis. The microbiology studies included examination of the spectra of activity of tavaborole and characterization of the mycology and susceptibility of strains of *Trichophyton rubrum* and *Trichophyton mentagrophytes*, obtained from clinical isolates of subjects treated with tavaborole topical solution, 5% for 48 weeks.

The mechanism of action of tavaborole is inhibition of fungal protein synthesis. Tavaborole inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS). Tavaborole has been shown to be active against most strains of *Trichophyton mentagrophytes* and *Trichophyton rubrum*, both in vitro and in clinical infections. This information will be incorporated into product labeling.

As the clinical development program assessed only toenail onychomycosis, and the potential organisms and disease course differs for fingernail disease, only onychomycosis of the toenail appears supported by the application. Additionally, only data for toenail onychomycosis due to *Trichophyton rubrum* and *T. mentagrophytes* was deemed adequate for inclusion in labeling. [REDACTED] (b) (4)

There are no outstanding clinical microbiology issues beyond agreement on final labeling.

7. Clinical/Statistical- Efficacy

The Agency biostatistics review was conducted by Dr. Kathleen Fritsch, and the clinical review was conducted by Dr. Milena Lolic.

Dose selection for the pivotal clinical trials was chosen based on results from three open label Phase 2 trials and a double blind Phase 2 trial which included three strengths of tavaborole solution, 2.5%, 5%, and 7.5%, which were compared to vehicle control in subjects with onychomycosis.

Tavaborole solution 5% was selected for Phase 3 and evaluated in two Phase 3 studies with a dosing regimen of once daily treatment with for 48 weeks. Studies 301 and 302 were identically designed, randomized, double-blind, vehicle controlled studies of the efficacy and safety of tavaborole solution, 5% in the treatment of toenail onychomycosis. Protocol 301 was submitted as a Special Protocol Assessment (SPA) on 8/14/2010, and an agreement letter was issued on 9/13/2010. The Agency and the applicant reached agreement on the study design and endpoints. Study 301 was conducted in the U.S. and Mexico. Study 302 was conducted in the U.S. and Canada.

Study 301 randomized 400 tavaborole and 194 vehicle subjects (one tavaborole subject was randomized in error and did not receive medication). Study 302 randomized 399 tavaborole and 205 vehicle subjects (three tavaborole subjects were randomized in error and did not receive medication). Both studies enrolled subjects age 18 and older with 20-60% involvement of the target toenail, positive culture, and positive KOH. About 82% of the subjects were male.

The primary efficacy endpoint was complete cure (0% clinical involvement of target toenail plus negative KOH and negative culture) at Week 52.

The secondary endpoints were (1) completely clear or almost clear target nail at Week 52, (2) treatment success (completely clear or almost clear target nail and negative mycology) at Week 52, and (3) negative mycology (negative KOH and negative culture). The 'other' efficacy endpoints were (1) change from baseline in the proportion of other nails (not including the target nail) that were completely clear or almost clear at Week 52, and (2) durability of clinical benefit from Week 52 to Week 60.

Tavaborole solution 5% was superior to vehicle on the primary efficacy endpoint of complete cure at Week 52 for the treatment of onychomycosis in two adequate and controlled trials. Dr. Fritsch summarized the Agency analyses as follows:

Table 1 – Primary and Secondary Efficacy Endpoints at Week 52

	Study 301			Study 302		
	Tavaborole N = 399	Vehicle N = 194	p-value	Tavaborole N = 396	Vehicle N = 205	p-value
<i>Primary Endpoint</i> Complete Cure	26 (6.5%)	1 (0.5%)	0.001	36 (9.1%)	3 (1.5%)	<0.001
<i>Secondary Endpoints</i>						
Completely Clear or Almost Clear Nail	104 (26.1%)	18 (9.3%)	<0.001	109 (27.5%)	30 (14.6%)	<0.001
Treatment Success*	61 (15.3%)	3 (1.5%)	<0.001	71 (17.9%)	8 (3.9%)	<0.001
Negative Mycology	124 (31.1%)	14 (7.2%)	<0.001	142 (35.9%)	25 (12.2%)	<0.001

*Completely clear or Almost Clear Nail + Negative Mycology

The secondary endpoint outcomes are consistent with the primary efficacy outcome, and all three were statistically significant in both studies when tested in sequential order.

Treatment effects were generally consistent across gender, race, age, and country subgroups in Studies 301 and 302.

The trials were conducted in accordance with Agency advice and agreements based on the SPA review. While the treatment effect was not large, statistical demonstration of efficacy was achieved. There are no outstanding issues related to efficacy beyond agreement on product labeling.

8. Safety

The applicant presented an adequate safety database consisting of 12 clinical trials/studies in which a total of 1500 subjects received at least one dose of tavaborole. Safety data were reviewed by Dr. Milena Lolic and included the following trials that utilized to-be-marketed formulation: two pivotal trials, three phase 2 trials, one pharmacokinetic, one dermal safety trial, and one QT/cardiovascular safety trial.

Safety assessment was based primarily on two phase 3 vehicle-controlled trials conducted in the United States, Mexico and Canada and comprised of 1186 subjects (791 randomized to tavaborole and 295 subjects randomized to vehicle). The safety evaluation consisted of reported adverse events, local tolerability assessments, vital signs, laboratory tests, and EKG data. Demographic characteristics between the groups in the trials were comparable and reflected the prevalence of this condition in general population.

Overall exposure in these trials was affected by several factors including variable number of treated toes, drop-out rate and missed doses. In general, however, the degree of variability did

not have significant impact on Dr. Lolic's review conclusions. The drop-out rate from safety population was about 13% and similar for both arms. The mean amount of study product (grams) used in the two studies was around 108 to 110 g in the two tavaborole arms, and 112 to 115 g in the two vehicle arms.

Approximately 58-64% of tavaborole and 54-70% of vehicle subjects experienced at least one adverse event, and approximately 2-3% of tavaborole and 1-4% of vehicle subjects experienced a serious adverse event. Approximately 1-3% of tavaborole subjects and 0.5-2% of vehicle subjects discontinued treatment due to adverse events.

There was one death reported in a phase 2 dose ranging trial. The cause was head trauma secondary to a fall. This was judged by the applicant and this reviewer to be unrelated to the drug treatment.

The incidence of serious adverse events (SAEs) was similar between subjects treated with tavaborole solution, 5% and vehicle (2.5% versus 2.4%, respectively). None of the SAEs appeared to be related to tavaborole in the opinion of the applicant as well as Dr. Lolic, the clinical reviewer.

Systemic exposure of tavaborole solution 5% is low and no systemic toxicities have been identified. As noted above, QTc related effects were not noted in the development program for this new molecular entity. There were no clinically meaningful changes observed in vital signs, laboratory values, or EKGs compared to vehicle.

The most common adverse reactions were application site reactions (7%) and ingrown toenail (3%). Subjects on the tavaborole arm had a higher rate of application site adverse reactions than subjects on the vehicle arm, including application site exfoliation (2.7% vs. 0.3%), application site erythema (1.6% vs. 0%), application site dermatitis (1.3% vs. 0%), and application site pain (1.0% vs. 0.3%).

No trials with tavaborole were conducted in pregnant women and women of childbearing potential. Subjects who enrolled in any of the clinical trials were required to use an effective form of birth control. Pregnancy was reported for three women participating in clinical studies (none in pivotal trials), two of which resulted in delivery of healthy children and one was lost to follow up. Pregnancy category C is recommended for labeling.

This CDTL review concurs with the conclusion of the primary medical officer review that the local safety issues identified, with the demonstration of efficacy described above, represent an overall acceptable risk benefit determination adequate to support an approval action for this application.

9. Advisory Committee Meeting

The review team determined early in the application review cycle that this new oxaborole antifungal, though an NME, presented no novel or complex regulatory issues that required the input of an advisory committee. None was conducted for this application.

10. Pediatrics

The applicant initially proposed [REDACTED] (b) (4)

[REDACTED] Following review of the literature, and submitted incidence/prevalence data for onychomycosis, the Division advised a waiver under age 12 years, and recommended an adolescent PK/safety trial for a population of ages 12-17, consistent with other recent advice to other sponsors. Studies under 12 years of age seem highly impractical due to the small number of pediatric subjects who would have documented fungal mycology.

DDDP proposed a pharmacokinetic/safety trial in 40 pediatric subjects age 12-17 years and 11 months with onychomycosis of toenails. This trial includes assessment of PK under maximal use conditions in a subgroup of at least 16 evaluable subjects. The applicant has agreed to conduct such a trial, and a waiver under age 12 years of age is recommended.

11. Other Relevant Regulatory Issues

No issues related to financial disclosures, GCP issues, or patent issues were identified in the review of the application.

GMP inspections are complete, and there are no outstanding issues impacting approval from the Office of Compliance. The Office of Compliance has made an overall "Acceptable" recommendation for the facilities involved in this NDA.

The Division of Scientific Investigators (DSI) was consulted to review the conduct of both clinical trials, and included the inspections of site 301-122 in Baltimore, MD and site 302-325 in Evansville, IN. Both sites were selected by the Division based on high number of patients enrolled and the high number of treatment responders. DSI inspections of the trial sites have been successfully completed, and the trial sites were deemed adequate.

12. Labeling

The trade name of “Kerydin” has been accepted by Office of Medication Error Prevention and Risk Management in their review dated January, 2014. The ONDQA recommendation is to add “topical” to the name of the product in labeling in accordance with recent USP recommendations to minimize dosage form confusion.

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. Final agreement on Agency proposed labeling, including carton/container labeling, is pending as of the date of this CDTL review. The applicant is aware of the Agency recommendations regarding the (b) (4) indication for product labeling of “toenail onychomycosis caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.”

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The conclusion of the clinical review, and that of the review team, and concurred by this CDTL review, is that safety and efficacy of tavaborole topical solution 5% is adequately demonstrated by the clinical development program. An approval action is recommended pending successful completion of ongoing labeling negotiations.

- Risk Benefit Assessment

Efficacy for toenail onychomycosis has been adequately demonstrated by the applicant in two trials. The safety findings are uncommon and largely limited to local adverse events, with no serious adverse events deemed related to the proposed topical product. Limited systemic absorption was noted and systemic adverse reactions are not expected. While the demonstrated treatment effect is relatively modest,

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

To address PREA requirements, a Post Marketing Requirement (PMR) for an adolescent pharmacokinetic/safety trial of tavaborole topical solution, 5% in pediatric subjects age 12-17 years with onychomycosis of toenails was recommended by the review team and has been accepted by the applicant.

- Recommended Comments to Applicant

There are no other recommended comments beyond the PMR/PMC listed above and draft labeling which has been conveyed to the applicant. Labeling negotiations are ongoing with the applicant as of the date of this review, but there are only minor differences to be resolved at this time.

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/s/

DAVID L KETTL
05/06/2014