CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204427Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Tatiana Oussova, M.D., M.P.H.
Subject	Deputy Division Director for Safety Summary Review
NDA/BLA # **Supplement #**	NDA 204427
Applicant Name	Anacor Pharmaceuticals, Inc.
Date of Submission	July 29, 2013
PDUFA Goal Date	July 29, 2014
Proprietary Name / **Established (USAN) Name**	Kerydin (tavaborole)
Dosage Forms / Strength	Topical solution 5%
Proposed Indication(s)	Treatment of onychomycosis of the toenail due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Milena Lolic, M.D.
Statistical Review	Kathy Fritsch, Ph.D.
Pharmacology Toxicology Review	Barbara Hill, Ph.D.
CMC Review/OBP Review	Gene W. Holbert, Ph.D.
Microbiology Review	Kerian Grande Roche, Ph.D.
Clinical Pharmacology Review	Angela Lu, Ph.D.
DDMAC	
OSI	Roy Blay, Ph.D.
CDTL Review	David Kettl, M.D.
OSE/DMEPA	Carlos M Mena-Grillasca, RPh
OSE/DDRE	
OSE/DRISK	Nyedra W. Booker, Pharm.D., M.P.H.
CDTL Review	David Kettl, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This is a 505 (b)(1) new drug application for a new molecular entity (NME), tavaborole, submitted by Anacor Pharmaceuticals, Inc. for the proposed indication: " the treatment of onychomycosis [redacted] (b) (4) However, the data submitted support [redacted] (b) (4) indication: " the treatment of toenail onychomycosis caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes".* This application has been reviewed under the PDUFA V Program.
Tavaborole is an oxaborole, the first in a new class of antifungal agents. It is a topical solution for an application to an affected toenail.
There was a recent approval (June 2014) of another topical antifungal product Jublia (eficonazole) for a similar indication. However, prior to that the last approval of a topical product for the treatment of onychomycosis of a toenail was issued to Penlac (ciclopirox) in 1999.
Tavaborole has not been approved in any other countries.
The Applicant proposed proprietary name KERYDIN was found acceptable.

There are no outstanding clinical or regulatory concerns. All discipline reviews have been completed and approval is recommended. There were no disagreements within the review team. There were a few disagreements between the Applicant and the review team on labeling issues that have been resolved. This review will provide more details on those issues and will briefly summarize the review team conclusions and my concurrence with the approval recommendation.

2. Background

The Applicant opened an IND for tavaborole in 2005 with a pharmacokinetic study. Since then, the Agency had multiple interactions with the Applicant, including EOP2 meeting in 2009, Guidance Meeting in 2012 and pre-NDA meeting in May of 2013.

Request for a special protocol assessment (SPA) was received on August 4, 2010 and the Agreement Letter was sent to the Applicant on September 13, 2010. Pivotal clinical studies were conducted according to the agreement.

Onychomycosis is a chronic fungal infection of toenails and/or fingernails. It is estimated that 15-20% of persons in United States between 40 and 60 years old have onychomycosis. It is more prevalent in adults than in children (prevalence rate 0.2% to 2.6%). The most common site of infection is the toenail. The most common type of toenail onychomycosis is distal subungual onychomycosis and the most common dermatophytes causing distal subungual onychomycosis are *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Fingernail onychomycosis is more likely to be caused by yeasts, most commonly *Candida albicans.*

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. Symptoms include toenail discomfort when walking, pain and social embarrassment.
Without treatment, the disease can cause progressive damage to the nail unit, and can spread to infect other nails, the skin, or potentially predispose to secondary bacterial infections (in immunocompromised populations). The criteria for diagnosis of onychomycosis include clinical evaluation, potassium hydroxide (KOH) microscopic evaluation, and fungal culture.

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.*

Tavaborole should be applied to the entire nail surface and under the tip of each nail being treated once daily for 48 weeks.

3. CMC/Device

KERYDIN topical solution, 5% is an alcohol/propylene glycol based clear, colorless solution containing 5% tavaborole (w/w).
The product is packaged with a (b) (4) dropper assembly, which is used to apply the product to the affected nail. The dropper assembly consists of a clear glass straight-tip pipette fitted with a rubber squeeze bulb and a black (b) (4) closure.
The proposed drug product specification includes tests and acceptance criteria for the following attributes: description, identity, tavaborole assay, impurities, EDTA assay, packaging integrity, weight loss, minimum fill, and microbiological testing.

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. The stability data support the proposed expiration dating period of 24 months for tavaborole solution when stored at 20-25 ºC (68-77 ºF).

The product is flammable and it is reflected in the label.

There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology data for this application was reviewed by Barbara Hill, Ph.D. Dr. Hill concluded that "the toxicity profile of tavaborole solution has been well characterized by the nonclinical studies conducted by the sponsor. There is no significant

safety concern for tavaborole solution at the proposed clinical dose". The most notable adverse effect was dose-dependent dermal irritation at the application site.
Dr. Hill recommended approval for this application.

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

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology data was reviewed by An Chi Lu, Ph.D. PK data was assessed in maximal use study of 24 subjects with toenail onychomycosis. Tavaborole undergoes extensive metabolism and renal excretion is the major route of elimination. No formal drug-drug interaction studies were conducted. In vitro studies and induction studies indicated that tavaborole is not likely to induce the activity of CYP450 enzymes.

The Applicant proposed (b) (4) Section 12.1, Mechanism of Action. Both Clinical and PK teams disagree with this proposal. In clinical trials the product was applied onto entire nail surface including under the tip of the nail therefore the clinical effect is due to penetration of the drug through different structures, (b) (4) . The Applicant has agreed to this rationale.

The Applicant did not conduct PK studies in pediatric population therefore the PREA PMR will be issued with the approval letter requiring the Applicant to conduct maximal use study in pediatric patients ages 12 to 17 year 11 months with onychomycosis of toenails.
Dr. Lu recommended approval for this application.

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

6. Clinical Microbiology

Clinical microbiology review was conducted by Kerian Grande Roche, Ph.D.
This review was critical for this application as the Applicant proposed a (b) (4) for the treatment of onychomycosis (b) (4) . Mycological testing (fungal culture and KOH wet mount) was performed in five Phase 2 and two Phase 3 studies of subjects with 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. Tavaborole has been shown to be active against most strains of *Trichophyton mentagrophytes* and *Trichophyton rubrum*, both in vitro and in clinical infections. Given that clinical development program only evaluated subjects with toenail onychomycosis plus supporting data from microbiology testing, only data for toenail

onychomycosis due to *Trichophyton rubrum* and *T. mentagrophytes* were included in labeling. (b) (4)

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

7. Clinical/Statistical-Efficacy

Tavaborole solution was evaluated in a double-blind dose-ranging Phase 2 study, two open label cohort Phase 2 studies, where one dosing regimen cohort is fully enrolled before the next cohort is enrolled, and two identical vehicle-controlled Phase 3 studies. The Phase 2 studies evaluated dose levels of 1%, 2.5%, 5%, and 7.5% and various treatment regimens from once daily for 30 days followed by three times weekly for 150 days to once daily treatment for 360 days.

The Phase 3 studies evaluated tavaborole solution 5% with a dosing regimen of once daily treatment with for 48 weeks. Study 301 randomized 400 tavaborole and 194 vehicle subjects. Study 302 randomized 399 tavaborole and 205 vehicle subjects. Both studies enrolled subjects age 18 and older with 20-60% involvement of the target toenail, positive culture, and positive KOH. Subjects applied treatment once daily for 48 weeks. The primary efficacy endpoint was complete cure at Week 52 (0% clinical involvement of target toenail plus negative KOH and negative culture). The secondary efficacy endpoints were: (1) completely clear or almost clear target nail at Week 52 (≤10% involvement of the nail), (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). Secondary endpoints were analyzed in sequential order.

Tavaborole solution 5% was superior to vehicle in the treatment of onychomycosis in both studies. The complete cure rate for tavaborole vs. vehicle was 6.5% vs. 0.5% in Study 301 and 9.1% vs. 1.5% in Study 302. The secondary efficacy endpoints defined in the protocol were supportive of the primary endpoint. The primary and secondary efficacy endpoints were all statistically significant ($p \leq 0.001$).

Table 1 shows the Applicant proposed efficacy endpoints for labeling.

Table 1. Proposed 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
(b) (4)						

(b) (4)

The Applicant proposed to include [redacted] (b) (4) . Review team disagreed and proposed that [redacted] (b) (4) at Week 52 be included instead. The Applicant has accepted review team proposal.

Table 2 shows the final table with primary and secondary efficacy endpoints for labeling inclusion.

Table 2. Primary and Secondary Efficacy Endpoint at Week 52

	Trial 1		Trial 2	
Efficacy Variable	**KERYDIN N=399 n(%)**	**Vehicle N=194 n(%)**	**KERYDIN N=396 n(%)**	**Vehicle N=205 n(%)**
Complete Cure[a]	26 (6.5%)	1 (0.5%)	36 (9.1%)	3 (1.5%)
Complete or Almost Complete Cure[b]	61 (15.3%)	3 (1.5%)	71 (17.9%)	8 (3.9%)
Mycologic Cure[c]	124 (31.1%)	14 (7.2%)	142 (35.9%)	25 (12.2%)

a. Complete cure defined as 0% clinical involvement of the target toenail plus negative KOH and negative culture.

b. Complete or almost complete cure defined as ≤10% affected target toenail area involved and negative KOH and culture.

c. Mycologic cure defined as negative KOH and negative culture.

8. Safety

The Applicant presented an adequate safety database consisting of 12 clinical trials in which a total of 1500 subjects received at least one dose of tavaborole. The safety evaluation consisted of reported adverse events, local tolerability assessments, vital signs, laboratory tests, and EKG data. 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.
Common adverse reactions occurring in ≥1% in subjects treated with KERYDIN included application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis.
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%). Systemic exposure of tavaborole solution 5% is low and no systemic toxicities have been identified. QTc related effects were not noted in the development program for this NME. There were no clinically meaningful changes observed in vital signs, laboratory values, or EKGs compared to vehicle.

Kerydin safety profile is similar to that of recently approved Jublia.

I concur with the review team recommendation that risk mitigation measures beyond professional labeling are not warranted for Kerydin (tavabarole) topical solution, 5%.

9. Advisory Committee Meeting

Tavaborole, a new oxaborole antifungal, though an NME, presented no novel or complex regulatory issues that required the input of an advisory committee.

10. Pediatrics

Safety and efficacy of Kerydin in pediatric subjects under the age of 18 years have not been studied as required under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).
The Applicant has requested a partial waiver to study Kerydin in pediatric age group <12 years of age. This request for partial waiver was granted because based on literature review, the prevalence of onychomycosis in subjects 12 years of age and younger is low and studies in this patient population would be impossible or highly impractical.

The applicant has requested a deferral of studies in pediatric subjects ages 12 to 17 years 11 months. A deferral was granted, as the adult studies are ready for approval and the pediatric study has not been completed.
The Applicant proposed the following timelines for the required maximal use PK trial:

Final Protocol Submission:	12/2014
Study Completion:	12/2018
Final Report Submission:	06/2019

The agency found these timelines acceptable. PREA PMR will be issued with the approval letter.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues

12. Labeling

There are no unresolved labeling issues.
Efficacy results for both pivotal trials are provided in Section 8, Efficacy.
Information that tavaborole topical solution is flammable is included in How Supplied/Storage and Handling Section of the labeling, Patient Counseling Information, and Patient Information.
Carton and immediate container labels were found to be acceptable.

13. Decision/Action/Risk Benefit Assessment

Recommended regulatory action: Approval

I concur with the review team conclusion that NDA 204427 for Kerydin (tavaborole) topical solution 5% be approved for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum or Trichophyton mentagrophyte.*

There is sufficient evidence of safety and efficacy to support use of Kerydin (tavaborole) topical solution, 5% as described in approved labeling.

No REMS or other risk management programs are recommended for this application.

This application is subject to PREA and will have a required pediatric assessment as described above under PEDIATRICS.

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/s/

TATIANA OUSSOVA
06/19/2014