CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director (acting) Decisional Memo

Date	July 7, 2014
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director (acting) Decisional Memo
NDA/BLA #	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 topical solution, 5%
Dosage Forms / Strength	Topical solution (43.5 mg/mL) in a 12 mL bottle containing 10 mL of solution, with an accompanying glass pointed-tip dropper
Proposed Indication(s)	For the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*.
Action:	Approval

Summary

Onychomycosis is a chronic fungal infection of the 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, including thickening, brittleness, and discoloration. Risk factors for the development of onychomycosis include older age, tinea pedis, and immunodeficiency. It is estimated that 15-20% of persons in the U.S. between the ages of 40 and 60 years old have onychomycosis.[1]

The most common site of infection is the toenail, and the most common type of toenail onychomycosis is distal subungual onychomycosis. The most common pathogens for toenail onychomycosis are *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

FDA-approved treatments for onychomycosis include both systemic (griseofulvin, itraconazole, terbinafine) and topical (ciclopirox, efinaconazole) therapies; however, efficacy rates are low. Systemic therapies achieve efficacy rates in the range of 14-38%, while topical therapy is associated with about an 8-14% efficacy rate. Currently approved systemic therapies are also associated with tolerability issues and toxicities, including drug-drug interactions and hepatotoxicity. Therefore, there is a need for additional therapeutic options for the treatment of toenail onychomycosis.

The subject of this NDA, tavaborole, is a first-in-class oxaborole antifungal with a molecular weight of approximately 151.93 Da. Its mechanism of action is inhibition of fungal protein synthesis through inhibition of an aminoacyl-transfer ribonucleic acid synthetase.

This memo documents my concurrence with the Division of Dermatology and Dental Products' (DDDP) approval recommendation for Kerydin (tavaborole) topical solution, 5% for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

Dosing

Tavaborole is available as a clear, colorless alcohol-based solution in 12 mL amber glass bottles containing 10 mL of solution, to be administered topically. Tavaborole is recommended to be applied to the entire surface and under the tip of each toenail being treated once daily for 48 weeks.

The Office of Clinical Pharmacology agrees that the proposed dosage strength appears appropriate based on Phase 2 data which demonstrated greater efficacy with tavaborole 5%

[1] Ghannoum MA, Hajjeh RA et al. A large-scale North American study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol 2000;43:641-648.

relative to either tavaborole 2.5% or 7.5%, and a better safety profile relative to tavaborole 7.5%.

Regulatory History

The IND for tavaborole was opened in 2005. There were multiple interactions with the applicant throughout the clinical development program. Of note were an End of Phase 2 meeting (October 2009), a Special Protocol Assessment agreement (September 2010), and a pre-NDA meeting (May 2013).

NDA 204427 was submitted on July 29, 2013 and granted a standard review with a user fee goal date of July 29, 2014.

Product Quality Considerations

There are no product quality issues that preclude approval of tavaborole. Adequate Chemistry Manufacturing and Controls (CMC) information was provided to assure the identity, strength, purity, and quality of the drug product.

Stability data support an expiration period of 24 months when stored at 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F). In-use study data support an in-use period of three months for the drug product. Patient labeling will caution the patient to discard product within 3 months after insertion of the dropper.

The product is flammable; this will be conveyed in product labeling.

All facilities involved in the manufacturing of tavaborole were evaluated by the Office of Compliance who issued an overall acceptable recommendation.

Methods validation was conducted by the Division of Pharmaceutical Analysis, who determined that the methods were acceptable for control and regulatory purposes.

The Office of New Drug Quality Assurance concurred with the applicant's request for a categorical exclusion from environmental assessment under 21 CFR 25.31(b).

No CMC post-marketing commitments (PMC) have been recommended.

Microbiology Product Quality Considerations

The New Drug Microbiology Staff in the Office of Pharmaceutical Science agreed with the applicant's proposal to waive microbial limits testing for product release and stability, as the product is inherently antimicrobial, and the applicant has performed suitable microbiological testing during development.

Non-clinical Considerations

Repeat dose oral toxicity studies with tavaborole were conducted in rats (up to 6 months) and repeat dose dermal toxicity studies with tavaborole solution were conducted in minipigs (up to 9 months). The target organ of toxicity in the oral rat toxicity studies was the nonglandular stomach, which is absent in humans. The target organ of toxicity in the dermal minipig toxicity studies was the skin, which exhibited a dose dependent increase in the incidence and severity of dermal irritation.

Tavaborole exhibited no evidence of mutagenic or clastogenic potential based on the results of *in vitro* (Ames assay and Human lymphocyte chromosomal aberration assay), and *in vivo* (rat micronucleus assay) genotoxicity testing.

An oral carcinogenicity study was conducted in Sprague-Dawley rats. No drug-related neoplastic findings were observed at oral doses up to 14 times the maximum recommended human dose (MRHD) based on area under the curve (AUC) comparison.

A dermal carcinogenicity study was conducted in CD-1 mice. No drug-related neoplastic findings were observed at doses up to 89 times the MRHD based on AUC comparison.

The potential reproductive toxicity of tavaborole 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 effects on fertility were observed in male and female rats administered oral doses up to 107 times the MRHD prior to and during early pregnancy.
- In the oral embryofetal development study in rats, in the presence of maternal toxicity, embryofetal toxicity (increased embryofetal resorption and/or deaths) and treatment-related skeletal malformations and variations suggestive of delayed development (delayed ossification) were observed in fetuses at doses up to 570 times the MRHD.
- In the oral embryofetal development study in rabbits, in the presence of maternal toxicity, excessive embryofetal mortality due to post-implantation loss was noted at 155 times the MRHD. No drug-related malformations were noted in rabbits at this exposure.
- In a dermal embryofetal development study in rabbits, topical doses of tavaborole 5% and 10% elicited dose dependent increases in dermal irritation at the treatment site. No drug-related malformations were noted in rabbits at 36 times the MRHD, and no embryofetal toxicity was noted in rabbits at 26 times the MRHD.

- In an oral pre- and post-natal development study in rats, in the presence of minimal maternal toxicity, no embryofetal toxicity or effects on postnatal development were noted at 29 times the MRHD.

Tavaborole was slightly irritating to intact rabbit skin after a single 24-hour topical application under occlusion and was an ocular irritant in rabbits. Tavaborole was classified as a non-sensitizer in guinea pigs. The need for a non-clinical photo-irritation study was waived for tavaborole solution since no absorption was noted within the range of sunlight.

No PMCs or post-marketing requirements (PMRs) have been recommended. Due to the observed teratogenic effects in animals, Kerydin will be labeled as a Pregnancy Category C and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Pharmacology Considerations

Tavaborole undergoes extensive metabolism. Renal excretion is the major route of elimination.

The PK of the to-be-marketed preparation of tavaborole 5% was assessed in Trial P06118 at Day 1 (after a single dose) and at Day 18 (after multiple doses) in 24 subjects with distal subungual onychomycosis. On Day 1, the mean C_{max} of tavaborole was 3.54 ± 2.26 ng/mL, the median T_{max} was 12 hours, and the mean AUC_{last} was 44.4 ± 25.5 ng*hr/mL. On Day 18, the mean C_{max} was 5.17 ± 3.47 ng/mL, the median T_{max} was 8.03 hours, and the mean AUC_{τ} was 75.8 ± 44.5 ng*hr/mL. Steady state was achieved after 14 days of dosing.

A thorough QT/QTc study was performed for tavaborole and was reviewed by the Interdisciplinary Review Team for QT Studies. The study doses included a therapeutic dose and a supratherapeutic dose which covered a margin of up to a 10- to 21-fold increase in the mean C_{max} over the therapeutic dose. The largest upper bounds of the 2-sided 90% confidence interval for the mean differences between tavaborole and placebo were below 10 msec. Therefore, at therapeutic doses, Kerydin is not expected to prolong QTc to any clinically relevant extent.

The drug-drug interaction potential of tavaborole was assessed in *in vitro* inhibition and induction studies. At therapeutic concentrations, tavaborole neither inhibits nor induces cytochrome P450 enzymes.

No PK data were provided in pediatric subjects. The Office of Clinical Pharmacology has recommended a PMR for a PK/safety study of Kerydin topical solution, 5% in pediatric subjects age 12-17 years and 11 months with onychomycosis of the toenails to include PK assessments in at least 16 evaluable subjects under maximal use conditions.

Clinical Microbiology

The Division of Anti-Infective Products reviewed microbiological studies submitted in the NDA. These included studies to determine mechanism of action, mechanism of resistance, spectrum of antimicrobial activity, and comparison to commercially available antifungals approved for the treatment of onychomycosis, as well as mycological testing (fungal culture and KOH wet mount) performed in the Phase 2 and 3 trials.

The mechanism of action of tavaborole is inhibition of fungal protein synthesis through the inhibition of an aminoacyl-transfer ribonucleic acid synthetase. Tavaborole demonstrated activity against most strains of *Trichophyton rubrum* and *Trichophyton mentagrophytes*, both *in vitro* and in clinical infections. *Trichophyton rubrum* and *Trichophyton mentagrophytes* strains from isolates collected in the clinical trials have not demonstrated resistance following repeated exposure to tavaborole.

No PMRs or PMCs have been recommended.

Efficacy

The efficacy of Kerydin (tavaborole) topical solution, 5% was assessed in two randomized, double-blind, vehicle-controlled trials – Trials 301 and 302 – in subjects with a clinical and laboratory diagnosis of distal subungual onychomycosis affecting at least one great toenail. Both trials were conducted in male and female subjects ≥18 years of age. The primary endpoint for both trials was complete cure, defined as no clinical evidence of onychomycosis of the target toenail and negative mycology (KOH and culture) of the target toenail, at Week 52.

The mean age of enrolled subjects in the trials was approximately 54 years. The majority of subjects were male (approximately 82%). Trial 301 was conducted in the U.S. (85% of subjects) and Mexico (15% of subjects). In Trial 301, approximately 79% of subjects were White and 5% were black; 26% of subjects were of Hispanic/Latino ethnicity. Trial 302 was conducted in the U.S. (80% of subjects) and Canada (20% of subjects). In Trial 302, approximately 90% of subjects were white and 5% were black; 14% were of Hispanic/Latino ethnicity.

In Trial 301, subjects were randomized to Kerydin (n=400) or vehicle (n=194) to be administered to all affected nails once daily for 48 weeks.

In Trial 302, subjects were randomized to Kerydin (n=399) or vehicle (n=205) to be administered to all affected nails once daily for 48 weeks.

In Trial 301, the complete cure rate in the intent-to-treat (ITT) population was 6.5% for Kerydin and 0.5% for vehicle, p=0.001. The results from the ITT and per protocol analyses were similar.

Table 1: Trial 301 – Complete Cure at Week 52

Population	Kerydin (%)	Vehicle (%)	p-value
ITT	26/399 (6.5)	1/194 (0.5)	0.001
PP	23/312 (7.4)	1/156 (0.6)	0.001

Secondary endpoints included:

- Completely clear or almost clear target nail at Week 52
- Treatment success (completely clear or almost clear target nail and negative mycology) at Week 52, and
- Negative mycology (negative KOH and negative culture)

The secondary endpoint outcomes were consistent with the primary efficacy outcome.

Table 2: Trial 301 – Secondary Efficacy Endpoints at Week 52

Endpoint	Kerydin N=399 n (%)	Vehicle N=194 n (%)	p-value
Completely Clear or Almost Clear	104 (26.1)	18 (9.3)	<0.001
Treatment Success	61 (15.3)	3 (1.5)	<0.001
Negative Mycology	124 (31.1)	14 (7.2)	<0.001

In Trial 302, the complete cure rate in the intent-to-treat (ITT) population was 9.1% for Kerydin and 1.5% for vehicle, p<0.001. The results from the ITT and per protocol analyses were similar.

Table 3: Trial 302 – Complete Cure at Week 52

Population	Kerydin (%)	Vehicle (%)	p-value
ITT	36/396 (9.1)	3/205 (1.5)	<0.001
PP	30/299 (10.0)	2/157 (1.3)	<0.001

Secondary endpoints included:

- Completely clear or almost clear target nail at Week 52
- Treatment success (completely clear or almost clear target nail and negative mycology) at Week 52, and
- Negative mycology (negative KOH and negative culture)

The secondary endpoint outcomes were consistent with the primary efficacy outcome.

Table 4: Trial 302 – Secondary Efficacy Endpoints at Week 52

Endpoint	Kerydin N=396 n (%)	Vehicle N=205 n (%)	p-value
Completely Clear or Almost Clear	109 (27.5)	30 (14.6)	<0.001
Treatment Success	71 (17.9)	8 (3.9)	<0.001
Negative Mycology	142 (35.9)	25 (12.2)	<0.001

The treatment effects were generally consistent across gender, race, age, and country subgroups in both trials.

The Office of Scientific Investigations (OSI) conducted inspections of two clinical sites that participated in the Phase 3 trials. A sponsor inspection of Anacor Pharmaceuticals, Inc. was also conducted. OSI concluded that the data generated by the clinical sites appear adequate in support of the proposed indication.

Safety

The safety of Kerydin focused on the two Phase 3 clinical trials where 791 subjects were exposed to Kerydin. The mean number of applications was 302 and 306 for the Kerydin arms, and 307 and 305 for the vehicle arms, in Trials 301 and 302, respectively.

In Trial 301, the proportion of subjects with at least one adverse event was 64% and 70% in the Kerydin-treated and vehicle-treated groups, respectively. In Trial 302, the proportion of subjects with at least one adverse event was 58% and 54% in the Kerydin-treated and vehicle-treated groups, respectively. The most common adverse reactions across both trials were application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis.

There was one death in the Kerydin clinical development program. The death was due to head trauma from a fall and is not considered treatment-related.

Serious adverse events (SAEs) were reported in 3% and 2% of Kerydin-treated and vehicle-treated subjects, respectively in Trial 301, and in 2% and 1%, respectively in Trial 302. None was considered to be treatment-related.

Adverse events leading to subject discontinuation from the trial occurred in <1% of Kerydin-treated subjects versus 1% of vehicle-treated subjects. Adverse events leading to treatment discontinuation occurred in 2% of Kerydin-treated subjects versus 1% of vehicle-treated

subjects. Treatment-related adverse events leading to subject discontinuation included application site erythema and application site exfoliation.

A cumulative irritancy study revealed the potential for Kerydin to cause skin irritation, but no evidence that Kerydin causes contact sensitization. This will be conveyed in product labeling.

Pediatric Considerations

The applicant requested a partial waiver for pediatric subjects <12 years of age. DDDP agreed with the waiver because based on review of the literature, DDDP concluded that the prevalence of onychomycosis in subjects <12 years of age is low and studies in this patient population would be impossible or highly impracticable to conduct.

The applicant requested a deferral of studies in pediatric subjects age 12 to 17 years 11 months. DDDP granted the deferral as the adult studies are ready for approval and the pediatric study has not been completed.

The applicant will conduct a PK/safety study of Kerydin topical solution, 5% in 40 pediatric subjects age 12-17 years and 11 months with onychomycosis of the toenails, as a PMR under the Pediatric Research Equity Act.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Office of Prescription Drug Products, has concluded that the applicant's proposed tradename "Kerydin" is acceptable. In a letter dated January 23, 2014, Anacor Pharmaceuticals, Inc. was notified that the proposed tradename was acceptable.

Advisory Committee

No Advisory Committee input was sought on this application. Although Kerydin is a New Molecular Entity, the application presented no novel or complex regulatory issues that required the input of an advisory committee.

Conclusion

A significant percentage of men and women in the 40-60 year-old age group in the U.S. have onychomycosis. Typical symptoms associated with toenail onychomycosis include toenail discomfort when walking, pain, and social embarrassment. Without treatment, the disease can progress, resulting in damage to the nail unit, and involvement of other nails, or the skin, potentially predisposing the individual to secondary bacterial infections, especially if the individual is immunocompromised. Additional topical therapies provide another option for individuals who cannot tolerate or cannot be prescribed systemic therapies.

Statistically significant albeit modest efficacy was demonstrated in two Phase 3 clinical trials with Kerydin topical solution, 5% administered daily for 48 weeks relative to vehicle control. No significant safety issues have been identified.

I concur with DDDP's recommendation for approval of Kerydin (tavaborole) topical solution, 5%, for the treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*, the PREA PMR detailed in this memo, and the agreed upon labeling.

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/s/

AMY G EGAN
07/07/2014