

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: April 7, 2014

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

Team Leader: Reema Mehta, Pharm.D., M.P.H., DRISK

Division Director: Claudia Manzo, Pharm.D., DRISK

Drug Name(s): Kerydin (tavaborole)

Subject: Review evaluates if a REMS is needed for Kerydin

Therapeutic Class: (b) (4) borinic acid complex anti-fungal

Dosage and Route: Topical Solution (5%), applied to affected nails

Application Type/Number: NDA 204-427

Applicant/sponsor: Anacor Pharmaceuticals, Inc.

OSE RCM #: 2013-1833

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1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the NDA 204-427 for Kerydin (tavaborole) topical solution (5%) to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). A 505(b)(1) application for Kerydin was received by the Division of Dermatology and Dental Products (DDDP) from Anacor Pharmaceuticals, Inc. on July 29, 2013, to treat onychomycosis (b) (4). The Sponsor did not propose a REMS for Kerydin.

1.1 PRODUCT BACKGROUND

Kerydin (tavaborole) is a (b) (4) boronic acid (5-fluoro-1, 3-dihydro-1-hydroxy-2, 1-benzoaxaborole) complex antifungal agent developed for the topical treatment of onychomycosis. Pharmacologic activity is achieved through the inhibition of fungal protein synthesis by inhibiting an aminoacyl-tRNA synthetase (aaRS) via an oxaborole-tRNA trapping mechanism¹, making Kerydin first in a new class of aaRS inhibitors for treating fungal infections.

Kerydin is a low molecular weight, alcohol (b) (4) based, 5% (w/w) topical solution developed to provide sufficient penetration through the nail plate to the nail bed in patients with onychomycosis of the toenails due to the dermatophytes *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

Recommended dosage and administration of Kerydin is as follows:

- Apply Kerydin to affected nails once daily for 48 weeks.
- Kerydin should be applied to the entire nail surface and under the tip of each nail being treated.

Kerydin is for topical use only and not for oral, ophthalmic, or intravaginal use.

1.2 DISEASE BACKGROUND

Onychomycosis² is a common fungal nail infection with a reported incidence of 2-13% in North America. While most cases are caused by dermatophytes and limited to toenail involvement, infection may also occur in the fingernails. Dermatophytic onychomycosis can be categorized as “distal subungual”, “proximal subungual”, and “white superficial.” Distal and proximal subungual onychomycosis most often result from *Trichophyton rubrum*, while white superficial onychomycosis is usually caused by *Trichophyton*

¹ Mechanism involves the “formation of an adduct with tRNA^{Leu} in the editing site of leucyl-tRNA synthetase” (Clinical Overview submitted for NDA 204-427).

² Onychomycosis is also referred to as *tinea unguium*, toenail fungus or dermatophytosis of nails.

mentagrophytes.³ Older age, tinea pedis, and immunodeficiency are some of the risk factors for acquiring onychomycosis.

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 pain and other toenail discomfort when walking. Social embarrassment may also develop.

Treating onychomycosis can be challenging, as topical creams and lotions are often unable to sufficiently penetrate the nail plate, and oral agents may be associated with numerous potential drug interactions and severe systemic adverse effects.⁴ Currently approved treatment options for onychomycosis include topical ciclopirox, oral griseofulvin, oral itraconazole, or oral terbinafine. Of the approved treatment options, none are marketed under a REMS program.

1.3 REGULATORY HISTORY

May 29, 2013: DDDP informed Anacor Pharmaceuticals, Inc at a pre-NDA meeting that they were not aware of any serious safety issues at that time that would necessitate a REMS.

July 26, 2013: Anacor Pharmaceuticals, Inc submitted 505(b)(1) NDA for Kerydin topical solution, 5%.

2 MATERIALS REVIEWED

The following are a list of materials used to inform the review:

- DDDP Clinical Review (M. Lolic), dated March 27, 2014
- Division of Anti-Infective Products, Clinical Microbiology Review (K. Grande Roche), dated March 6, 2014
- Draft Labeling for Kerydin, dated February 18, 2014
- Discipline specific mid-cycle reviews for Kerydin, dated December 13, 2013
- Anacor Pharmaceuticals, Inc. Clinical Overview for Kerydin (NDA 204-427), dated July 29, 2013
- Anacor Pharmaceuticals, Inc. Summary of Clinical Safety for Kerydin (NDA 204-427), dated July 29, 2013
- Pre-NDA meeting minutes for IND 071-206, dated June 3, 2013

³ (2013). Chapter 193. Onychomycosis. In Usatine R.P., Smith M.A., Chumley H.S., Mayeaux E.J., Jr. (Eds), *The Color Atlas of Family Medicine, 2e*. Retrieved March 13, 2014 from <http://accessmedicine.mhmedical.com/content.aspx?bookid=685&Sectionid=45361264>.

⁴ Botek, G. (2003). Fungal nail infection: Assessing the new treatment options. *Cleveland Clinic Journal of Medicine*, 110-118.

3 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for Kerydin included 12 clinical studies (three Phase 2 studies, two Phase 3 studies, one safety pharmacology, two clinical pharmacology, and four pharmacokinetic studies) involving 1966 subjects (1589 patients with onychomycosis and 377 healthy volunteers). The following pivotal Phase 3 studies formed the basis of safety and efficacy analyses:

Studies S-301 and S-302	
Study Design	Randomized (2:1 ratio), double-blind, vehicle-controlled, multi-center study
Inclusion Criteria	Adults with a clinical diagnosis of distal, subungual, onychomycosis affecting at least one great toenail. Disease severity defined as 20-60% involvement of the target nail after the nail had been trimmed, with at least 3mm clear nail measured from the proximal nail fold. Clinical diagnosis confirmed by positive KOH and positive fungal culture.
Treatment protocol	Apply once daily to all affected nails for a 48-week treatment period. Subjects were required to apply at least 80% (and not more than 120%) of the expected doses and not miss more than 14 consecutive days of treatment.
Primary endpoint	“Complete Cure” at Week 52 (defined as no clinical evidence of onychomycosis, negative KOH and negative fungal culture)
Treatment arms, sample size and study location	S-301 (US and Mexico): <ul style="list-style-type: none"> • Kerydin (N=400); Vehicle (N=194) S-302 (US and Canada): <ul style="list-style-type: none"> • Kerydin (N=399); Vehicle (N=205)

3.1 EFFICACY

The primary efficacy endpoint (proportion of subjects with complete cure of toenail onychomycosis at Week 52) was met in both pivotal studies. Kerydin solution (5%) was statistically and clinically more effective than the vehicle in providing a “Complete Cure” at Week 52, with cure rates of 7% in subjects treated with Kerydin in S-301 and 9% in Kerydin-treated subjects in S-302. Complete Cure for vehicle-treated subjects was 1% and 2% for S-301 and S-302 respectively.

Efficacy of Kerydin versus vehicle was also demonstrated in both trials, for all three secondary endpoints ($p < 0.001$) as presented in Table 1.

Table 1: Secondary Efficacy Endpoints Analysis

Trial	Secondary Endpoints⁵	Kerydin 5%	Vehicle
S-301	Clear nail	104/399 (26%)	18/194 (9%)
	Treatment Success	61/399 (15%)	3/194 (2%)
	Negative mycology	124/399 (31%)	14/194 (7%)
S-302	Clear nail	109/396 (28%)	30/205 (15%)
	Treatment Success	71/396 (18%)	8/205 (4%)
	Negative mycology	142/396 (36%)	25/205 (12%)

⁵ Note: “Clear nail” defined as $\leq 10\%$ involvement of nail; “Treatment success” defined as $\leq 10\%$ involvement of nail AND negative mycology (negative KOH and culture)

DDDP Clinical Reviewer Comment: Treatment effects for each of the secondary points are higher than for primary endpoint and that could be explained by the more stringent criteria for the primary endpoint.

3.2 SAFETY

The safety population for Kerydin consisted of 1186 subjects who were randomized to receive Kerydin (791 subjects) or vehicle (295 subjects), received at least one confirmed dose of the investigational product, and had a least one post-baseline assessment. The safety evaluation consisted of the following: reported adverse events, local tolerability assessments, vital signs, laboratory tests, and electrocardiogram (EKG) data.

The most common adverse events (AEs) occurring in >2% of subjects receiving Kerydin (and at greater frequency than observed with vehicle) included upper respiratory infection, back pain, application site exfoliation, ingrown toenail, procedural pain, muscle strain and arthralgia. Systemic exposure to Kerydin was low, and no systemic toxicities were identified. There were also no clinically meaningful trends observed related to vital signs, laboratory values and EKG findings. One death was reported across all clinical trials and deemed unrelated to the study drug.

Severe, *treatment-related* AEs were reported in 7 subjects (5 in the Kerydin arm and 2 in the vehicle arm) and consisted of application site reactions (e.g., pain, discharge, edema, induration and exfoliation) and local skin reactions (e.g., contact dermatitis and pruritis). Most local skin reactions, however, were considered mild to moderate.

Kerydin's potential to cause irritation was tested in a randomized, single-blind, controlled trial of 45 healthy subjects. Kerydin produced a mean irritation response that was higher than the positive irritant control.⁶

4 DISCUSSION

Kerydin has the ability to penetrate the nail plate to the bed of infected nails, with low systemic absorption following topical application. If approved, Kerydin would represent the first in a new class of aaRS inhibitors. According to the DDDP clinical reviewer, Kerydin may be a reasonable option for patients with onychomycosis unable to tolerate oral antifungals, and who do not wish to undergo more comprehensive topical treatment required⁷ with Penlac[®], currently the only approved topical product in the U.S. to treat toenail onychomycosis. Penlac[®] Nail Lacquer (ciclopirox) Topical Solution, 8%, does not have REMS program requirements.

Kerydin has demonstrated clinical benefit in the treatment of onychomycosis due to the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*. The severe treatment related AEs consisted of application site reactions and local skin reactions, which is expected for topical products. The spectrum of application site reactions was limited to events such as exfoliation, induration, pain, etc. There are no serious risks

⁶ The potential of Kerydin to cause irritation was tested using Kerydin 5% solution, vehicle, positive irritant control (lauryl sulfate solution 0.5% w/v) and negative irritant control (0.9% saline for injection).

⁷ Penlac[®] requires up to 48 weeks of daily applications. Professional removal of the unattached, infected nail, as frequently as monthly, is considered the full treatment needed to achieve a clear or almost clear nail (defined as 10% or less residual nail involvement).

identified at this time to warrant a REMS. The professional labeling will include application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis as ADVERSE REACTIONS. In addition, the DDDP clinical reviewer recommended that Kerydin be labeled as an *irritant*.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Kerydin (tavabarole) topical solution, 5%. Kerydin has demonstrated efficacy in the treatment of onychomycosis. There were no serious risks of concern identified during the review of the application that required mitigation beyond labeling. Thus, the benefit-risk profile for Kerydin is favorable and the risks can be mitigated through professional labeling.

Should DDDP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

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/s/

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