HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KERYDIN safely and effectively. See full prescribing information for KERYDIN.

KERYDIN® (tavaborole) topical solution, 5%
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
KERYDIN is an oxaborole antifungal indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. (1)

----------DOSAGE AND ADMINISTRATION----------
- Apply KERYDIN to affected toenails once daily for 48 weeks. (2)
- KERYDIN should be applied to the entire toenail surface and under the tip of each toenail being treated. (2)
- For topical use only. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Solution, 5%. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Common adverse reactions occurring in ≥1% in subjects treated with KERYDIN included application site exfoliation, ingrown toenail, application site erythema, and application site dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Anacor Pharmaceuticals at 1-844-4ANACOR [1-844-426-2267] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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2 DOSAGE AND ADMINISTRATION

Apply KERYDIN to affected toenails once daily for 48 weeks.

KERYDIN should be applied to the entire toenail surface and under the tip of each toenail being treated.

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

3 DOSAGE FORMS AND STRENGTHS

KERYDIN topical solution, 5% is a clear, colorless alcohol-based solution. Each milliliter of solution contains 43.5 mg (5% w/w) of tavaborole.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two clinical trials, 791 subjects were treated with KERYDIN. The most commonly reported adverse reactions are listed below (Table 1).

Table 1: Adverse Reactions Occurring in ≥1% of KERYDIN Topical Solution, 5%-Treated Subjects and at a Greater Frequency than Observed with Vehicle

Preferred Term	KERYDIN N=791 n(%)	Vehicle N=395 n(%)
Application site exfoliation	21 (2.7%)	1 (0.3%)
Ingrown toenail	20 (2.5%)	1 (0.3%)
Application site erythema	13 (1.6%)	0 (0%)
Application site dermatitis	10 (1.3%)	0 (0%)

A cumulative irritancy study revealed the potential for KERYDIN to cause skin irritation. There was no evidence that KERYDIN causes contact sensitization.

7 DRUG INTERACTIONS

In vitro studies have shown that tavaborole, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with KERYDIN in pregnant women. KERYDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits and a dermal embryofetal development study was conducted in rabbits.

Oral administration:
In an oral embryofetal development study in rats, oral doses of 30, 100, and 300 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal resorption and/or deaths) and drug-related skeletal malformations and variations suggestive of delayed development (i.e., a delay in ossification) were noted in fetuses at 300 mg/kg/day tavaborole [570 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons]. No developmental toxicity was noted in rats at 100 mg/kg/day tavaborole (26 times the MRHD based on AUC comparisons).

In an oral embryofetal development study in rabbits, oral doses of 15, 50, and 150 mg/kg/day tavaborole were administered during the period of organogenesis (gestational days 7-19) to pregnant female rabbits. In the presence of maternal toxicity, excessive embryofetal mortality due to post-implantation loss was noted at 150 mg/kg/day tavaborole. No drug related malformations were noted in rabbits at 150 mg/kg/day tavaborole (155 times the MRHD based on AUC comparisons). No embryofetal mortality was noted in rabbits at 50 mg/kg/day tavaborole (16 times the MRHD based on AUC comparisons).

Topical administration:
In a dermal embryofetal development study in rabbits, topical doses of 1%, 5%, and 10% tavaborole solution were administered during the period of organogenesis (gestational days 6-28) to pregnant female rabbits. A dose dependent increase in dermal irritation at the treatment site was noted at 5% and 10% tavaborole solution. A decrease in fetal bodyweight was noted at 10% tavaborole solution. No drug related malformations were noted in rabbits at 10% tavaborole solution (36 times the MRHD based on AUC comparisons). No embryofetal toxicity was noted in rabbits at 5% tavaborole solution (26 times the MRHD based on AUC comparisons).

Nonteratogenic effects:
In an oral pre- and post-natal development study in rats, oral doses of 15, 60, and 100 mg/kg/day tavaborole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of minimal maternal toxicity, no embryofetal toxicity or effects on postnatal development were noted at 100 mg/kg/day (29 times the MRHD based on AUC comparisons).

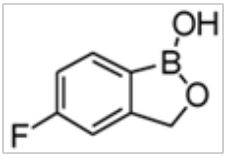
8.3 Nursing Mothers
It is not known whether tavaborole is excreted in human milk following topical application of KERYDIN. Because many drugs are excreted in human milk, caution should be exercised when KERYDIN is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
In clinical trials of 791 subjects who were exposed to KERYDIN, 19% were 65 years of age and over, while 4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

KERYDIN (tavaborole) topical solution, 5% contains tavaborole, 5% (w/w) in a clear, colorless alcohol-based solution for topical use. The active ingredient, tavaborole, is an oxaborole antifungal with the chemical name of 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. The chemical formula is $C_7H_6BFO_2$, the molecular weight is 151.93 and the structural formula is:



Tavaborole is a white to off-white powder. It is slightly soluble in water and freely soluble in ethanol and propylene glycol.

Each mL of KERYDIN contains 43.5 mg of tavaborole. Inactive ingredients include alcohol, edetate calcium disodium, and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KERYDIN is an oxaborole antifungal [see *Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

At therapeutic doses, KERYDIN is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

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

In a clinical pharmacology trial of six healthy adult male volunteers who received a single topical application of 5% ^{14}C-tavaborole solution, tavaborole conjugates and metabolites were shown to be excreted primarily in the urine.

The pharmacokinetics of tavaborole was investigated in 24 subjects with distal subungual onychomycosis involving at least 4 toenails (including at least 1 great toenail) following a single dose and a 2-week daily topical application of 200 µL of a 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail. Steady state was achieved after 14 days of dosing. After a single dose, the mean (± standard deviation) peak concentration (C_{max}) of tavaborole was 3.54 ± 2.26 ng/mL (n=21 with measurable concentrations, range 0.618-10.2 ng/mL, LLOQ=0.5 ng/mL), and the mean AUC_{last} was 44.4 ± 25.5 ng*hr/mL (n=21). After 2 weeks of daily dosing, the mean C_{max} was 5.17 ± 3.47 ng/mL (n=24, range 1.51-12.8 ng/mL), and the mean AUC_{τ} was 75.8 ± 44.5 ng*hr/mL.

12.4 Microbiology

Mechanism of Action

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).

Activity in vitro and in clinical infections

Tavaborole has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections [see *Indications and Usage (1)*]:

Trichophyton rubrum

Trichophyton mentagrophytes

Mechanism of Resistance
Trichophyton mentagrophytes and *Trichophyton rubrum* strains from isolates collected in the clinical trials have not demonstrated resistance following repeated exposure to tavaborole.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral carcinogenicity study in Sprague-Dawley rats, oral doses of 12.5, 25, and 50 mg/kg/day tavaborole were administered to rats once daily for 104 weeks. No drug related neoplastic findings were noted at oral doses up to 50 mg/kg/day tavaborole (14 times the MRHD based on AUC comparisons).

In a dermal carcinogenicity study in CD-1 mice, topical doses of 5%, 10%, and 15% tavaborole solution were administered to mice once daily for 104 weeks. No drug related neoplastic findings were noted at topical doses up to 15% tavaborole solution (89 times the MRHD based on AUC comparisons).

Tavaborole 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).

No effects on fertility were observed in male and female rats that were administered oral doses up to 300 mg/kg/day tavaborole (107 times the MRHD based on AUC comparisons) prior to and during early pregnancy.

14 CLINICAL STUDIES

The efficacy and safety of KERYDIN was evaluated in two multicenter, double-blind, randomized, vehicle-controlled trials. KERYDIN or vehicle was applied once daily for 48 weeks in subjects with 20% to 60% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement.

A total of 1194 subjects (795 KERYDIN, 399 Vehicle) 18 to 88 years of age, 82% male, 84% white, participated in these two trials. Efficacy assessments were made at 52 weeks following a 48-week treatment period.

The Complete Cure efficacy endpoint included negative mycology (negative KOH wet mount and negative fungal culture) and Completely Clear Nail (no clinical evidence of onychomycosis as evidenced by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis). Efficacy results from the two trials are summarized in Table 2.

Table 2: Efficacy Outcomes

	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%)

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