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APPLICATION NUMBER:

204427Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204427	Submission Date(s): 7/29/2013
Brand Name	Kerydin
Generic Name	Tavaborole Topical Solution, 5%
Primary Reviewer	An-Chi Lu, M.S., Pharm.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Anacor Pharmaceuticals Inc.
Submission Type	Original NDA
Formulation; Strength(s)	Topical Solution, 5%
Indication	For the topical treatment of onychomycosis (b) (4)

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1 Executive Summary

This application is for Kerydin (tavaborole) Topical Solution, 5%. Tavaborole is a new molecular entity (NME). The Sponsor has submitted this NDA via 505(b)(1) regulatory pathway, and the proposed indication for Kerydin (tavaborole) Topical Solution is for the treatment of onychomycosis. It is intended to be applied to the entire nail surface and under the tip of each nail being treated once daily for 48 weeks.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 204427 acceptable from a Clinical Pharmacology perspective, pending agreement on recommended labeling changes.

1.2 Phase IV Commitments/Requirements

Post Marketing Requirement (PMR) for a pharmacokinetic/safety trial of tavaborole topical solution, 5% in pediatric subjects age 12-17 years and 11 months with onychomycosis of toenails (b) (4)

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Systemic bioavailability:

Trial P06118 was 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 1 great toenail were treated with a single dose of tavaborole 5% solution (approximately 200 µL) 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} (± 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 AUCτ 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, it appears that steady state was reached on Day 11 after 6 days of daily dosing.

Based on the NOAEL level of 3% tavaborole solution determined in the 9-month dermal minipig toxicity study, the safety margin is 10.1 based on mean human AUCτ and 4.4 based on maximum human AUCτ.

Effects on QT interval:

From the review of Interdisciplinary Review Team for QT Studies Consultation, Dr.Moh Jee Ng has 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. For the supratherapeutic dose group, tavaborole topical solution, 5% was applied twice daily on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days to healthy subjects. Following the supratherapeutic dose, the mean C_{max} was 22.4 ± 14.3 ng/mL. Compared to the C_{max} of 5.17 ng/mL in the maximal use PK trial P06118 after 14 continuous days of once-daily dosing, the C_{max} obtained from supratherapeutic dose of this TQT trial was 4.3-times higher (range: 3.3-times to 6.5-times). With the supratherapeutic dose (applied to healthy subjects) achieving a C_{max} 4.3-times higher than the C_{max} observed in the maximal use PK trial, tavaborole does not prolong QTc to any clinically relevant extent.

Drug-Drug Interaction:
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 CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 or inhibit the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. The I/Ki ratio is calculated to be < 0.00068.

Pediatrics:
The sponsor did not provide any PK data for tavaborole topical solution, 5% in pediatrics. The sponsor is requesting a waiver of pediatric trials in pediatrics less than 12 years of age and deferral of pediatric trials in age range of 12-17 years and 11 months to be conducted post approval. The Division of Dermatology and Dental Products (DDDP) agrees with the waiver and deferral of pediatric trials. DDDP proposed a pharmacokinetic/safety trial in 40 pediatric subjects age 12-17 years and 11 months with onychomycosis of toenails (b) (4). This reviewer recommends that the trial includes assessment of PK under maximal use conditions in a subgroup of at least 16 evaluable subjects.

Clinical Pharmacology Briefing:
An optional intra-division level Clinical Pharmacology briefing was conducted on February 24, 2014 with the following in attendance: Hae-Young Ahn, Yow-Ming Wang, Doanh Tran, Chinmay Shukla, and An-Chi Lu.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for Tavaborole Topical Solution, 5%?

Tavaborole Topical Solution, 5% is proposed for the topical treatment of onychomycosis (b) (4)

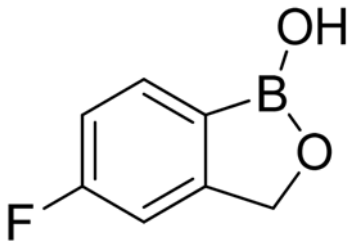
2.1.2 What is onychomycosis?

Onychomycosis is a fungal infection of the nail plate and other parts of the nail unit including the nail matrix. Dermatophytes are responsible for most finger and toenail infections, and Dermatophytic onychomycosis (tinea unguium) occurs in three distinct forms: distal and lateral subungual, proximal subungual, and superficial white. The vast majority of distal and proximal subungual onychomycosis results from Trichophyton rubrum. Superficial white onychomycosis is usually caused by T. mentagrophytes, although cases caused by T. rubrum have also been reported.
The prevalence in the United and States and Europe is up to 10% of adult population, and is related to occlusive footwear. The disease is very common in adults, but may also occur in children.

2.1.3 What are the highlights of the physicochemical properties of Tavaborole?

Chemically, tavaborole is 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or 5-fluoro-2,1-benzoxaborol-1(3H)-ol. Tavaborole has a molecular weight of 151.93 Daltons, and is a white to off-white powder.

The molecular formula of tavaborole is $C_7 H_6 B F O_2$. The structural formula is as follows:



Formulation properties:
Tavaborole Topical Solution, 5% is an alcohol/ (b) (4) based solution containing 5% tavaborole (w/w). The solution is filled to a minimum label amount of 10 mL in a 12 mL, amber USP (b) (4) glass bottle with an 18-400 neck finish and an 18-400 black (b) (4) closure with a (b) (4) foam liner. Each milliliter of Kerydin contains 43.5 mg of tavaborole (5% w/w). For details of product composition see section 2.5.2.

Dosage and Route of Administration:
Apply to affected nails once daily for 48 weeks. It should be applied to the entire nail surface and under the tip of each nail being treated.

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). Tavaborole has been shown to be active against most strains of Trichophyton mentagrophytes and Trichophyton rubrum, both in vitro and in clinical infections.

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