DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204427

WRITTEN REQUEST – AMENDMENT 1

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, M.Sc.
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Reference is made to your December 18, 2014 Proposed Pediatric Study Request for Kerydin (tavaborole) topical solution, 5%.

We are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on April 17, 2015, remain the same. (Text added is underlined. Text deleted is strikethrough.)

This study investigates the potential use of tavaborole in the treatment of pediatric population 6 years to 16~~17~~ years 11 months old with onychomycosis of the toenail caused by *Trichophyton rubrum* or *T. mentagrophytes*.

- *Clinical studies:*

Open-label pharmacokinetic/safety study of tavaborole topical solution, 5% in pediatric subjects aged 6 to 16~~17~~ years and 11 months with onychomycosis of the toenails. The PK assessments will be performed on a subset of at least 16 subjects under maximal use conditions. The protocol for this study must be agreed upon with the FDA prior to initiation.

- *Objective of the study:*

The objective of this study is to assess the safety and tolerability of KERYDIN topical solution, 5%, applied once daily to affected toenail for 48 weeks in pediatric subjects (aged 6 to 16~~17~~ years ~~of age~~ and 11 months) with mild to moderate onychomycosis of the toenails.

The secondary objective is to perform PK assessments in a subpopulation of subjects following topical administration under maximal use conditions for 4 weeks.

- *Patients to be Studied:*

  Subjects with distal subungual onychomycosis involving at least 20% of the total area of the target great toenail accompanied by a positive potassium hydroxide (KOH) wet mount and a positive fungal culture for the dermatophytes *Trichophyton rubrum* (*T. rubrum*) or *Trichophyton mentagrophytes* (*T. mentagrophytes*)

  Subjects included in the PK subgroup will be under maximal use conditions, including disease severity, application area, and dose. Enrollment should be approximately evenly distributed among ages for subjects ages 12 – 16~~17~~ years and 11 months of age and males and females and there should be a sufficient number of subjects 12 – 13 years of age.

  - *Age group in which study will be performed*: Subjects 6 years to 16~~17~~ years and 11 months.

  - *Number of patients to be studied:* At least 40 subjects 12 – 16~~17~~ years and 11 months of age out of which at least 16 evaluable subjects meet maximal use conditions.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated April 17, 2015, as amended by this letter, must be submitted to the Agency on or before February 28, 2018, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Cristina Attinello, MPH, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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WRITTEN REQUEST

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodriguez, M.Sc.
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
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Dear Ms. Rodriguez:

Reference is made to your December 18, 2014 Proposed Pediatric Study Request for Kerydin (tavaborole) topical solution, 5%.

BACKGROUND:

This study investigates the potential use of tavaborole in the treatment of pediatric population 6 years to 16 years 11 months old with onychomycosis of the toenail caused by *Trichophyton rubrum* or *T. mentagrophytes*.

Onychomycosis of the toenails is predominantly a disease of adults, however, there are several publications that describe various types of onychomycosis and treatment options in children[1,2,3]. In order to determine the age of children appropriate for an onychomycosis study, the Division has considered only data that are reflective of the recommended indication-onychomycosis of the toenail due to dermatophytes (*T. rubrum or T. mentagrophytes*) and determined that culture-positive onychomycosis is extremely low in patients less than 12 years of age, which was the reason for waiving PREA required studies in this subpopulation.

However, due to the lack of the specific safety concerns with Kerydin, and presence of sporadic onychomycosis cases in the younger pediatric age group, the Division requests opening enrollment to pediatric patients down to 6 years of age for the purpose of issuing this WR. There were no literature cases describing onychomycosis in neonates, therefore the study in this age group is not required.

[1] Gupta AK, Chang P et all. Onychomycosis in children: prevalence and management. Pediatric Dermatology 1998;15(6:464-471)
[2] Gupta AK, Paquet M Systemic antifungals to treat onychomycosis in children: a systemic review. Pediatric Dermatology 2012;1-9
[3] Finlay GH, Vismer HF et all. The spectrum of paediatric dermatology-analysis of 10,000 cases. British Journal of Dermatology 1974;91:379-387

Efficacy in the pediatric population can be extrapolated from adults because the course of the disease, the type of the microorganisms that cause onychomycosis and the effect of the drug are anticipated to be the same in adults and children.

To obtain needed pediatric information on tavaborole, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Open-label pharmacokinetic/safety study of tavaborole topical solution, 5% in pediatric subjects aged 6 to 16 years and 11 months with onychomycosis of the toenails. The PK assessments will be performed on a subset of at least 16 subjects under maximal use conditions. The protocol for this study must be agreed upon with the FDA prior to initiation.

- *Objective of the study:*

The objective of this study is to assess the safety and tolerability of KERYDIN topical solution, 5%, applied once daily to affected toenail for 48 weeks in pediatric subjects (aged 6 to 16 years and 11 months) with mild to moderate onychomycosis of the toenails.

The secondary objective is to perform PK assessments in a subpopulation of subjects following topical administration under maximal use conditions for 4 weeks.

- *Patients to be Studied:*

Subjects with distal subungual onychomycosis involving at least 20% of the total area of the target great toenail accompanied by a positive potassium hydroxide (KOH) wet mount and a positive fungal culture for the dermatophytes *Trichophyton rubrum* (*T. rubrum*) or *Trichophyton mentagrophytes* (*T. mentagrophytes*)

Subjects included in the PK subgroup will be under maximal use conditions, including disease severity, application area, and dose. Enrollment should be approximately evenly distributed among ages for subjects ages 12 – 16 years and 11 months of age and males and females and there should be a sufficient number of subjects 12 – 13 years of age.

  - *Age group in which study will be performed*: Subjects 6 years to 16 years and 11 months.

- *Number of patients to be studied:* At least 40 subjects 12 – 16 years and 11 months of age out of which at least 16 evaluable subjects meet maximal use conditions.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - ☐ *Pharmacokinetic Endpoints:*
    The pharmacokinetic endpoints for the study should include descriptive statistical analysis of steady state systemic concentrations of tavaborole.
  - ☐ Complete Cure must be assessed as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52.
  - ☐ Important secondary endpoints must include Complete or Almost Complete Cure at Week 52 (defined as ≤ 5% target toenail involvement), The Clinical Efficacy rate at Week 52, and The Mycological Cure rate at Week 52.
  - ☐ These assessments are intended to assess compliance with treatment for the purposes of the safety assessment.
  - ☐ *Safety Endpoints:* adverse events, vital signs, routine clinical laboratory testing.

- *Known Drug Safety concerns and monitoring:*
  Local adverse events (ingrown toenail and application site reactions e.g. burning/stinging, induration/edema, oozing and crusting, pruritus, erythema, and scaling)

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form:* solution
  - *route of administration:* topical
  - *Regimen:* once daily

- *Statistical information, including power of study and statistical assessments:*
  The study must each assess at least 40 subjects of which at least 16 evaluable subjects meet maximal use conditions. The reports should include descriptive summary statistics for all safety, efficacy, and pharmacokinetic assessments as agreed with the Agency at the time of protocol submission and review prior to initiation of the study.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that tavaborole is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before February 28, 2018. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6

months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information,* FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the

submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Cristina Attinello, MPH, Senior Regulatory Project Manager, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
07/10/2015