



NDA 208010

**NDA APPROVAL**

OPKO Ireland Global Holdings Ltd.  
C/o OPKO Health Inc.  
Attention: Jane Hsaio, Ph.D., MBA  
President and Director  
4400 Biscayne Blvd.  
Miami, FL 33137

Dear Dr. Hsaio:

Please refer to your New Drug Application (NDA) dated and received, May 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rayaldee (calcifediol) extended-release capsules.

This new drug application provides for the use of Rayaldee (calcifediol) extended-release capsules for the treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total hydroxyvitamin D levels less than 30 ng/mL.

We acknowledge receipt of your amendment dated April 22, 2016, which constituted a complete response to our March 28, 2016, action letter.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on April 22, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208010.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to 4 weeks because necessary studies are impossible or highly impracticable. This is because neonates are highly unlikely to be diagnosed with secondary hyperparathyroidism due to stage 3 and 4 chronic kidney disease and vitamin D insufficiency because it requires time after birth for the vitamin D insufficiency and secondary hyperparathyroidism to develop.

We are deferring submission of your pediatric studies for ages 1 month to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed, and because a new formulation suitable for use in the pediatric population must first be developed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3052-1 Conduct a repeat dose, dose ranging pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Rayaldee (calcifediol) in predialysis patients with stage 3 or 4 chronic kidney disease with secondary hyperparathyroidism and 25-OH vitamin D levels < 30 mcg/L and ages 1 month to less than 18 years. The study should include a minimum of 6 weeks of follow up to allow for the estimation of the calcifediol elimination.

Final Protocol Submission: March 2017  
Study Completion: September 2019  
Final Report Submission: March 2020

3052-2 Conduct a 16-week, randomized (1:1), placebo-controlled, double-blind, efficacy and safety study evaluating Rayaldee (calcifediol) in predialysis patients with stage 3 or 4 chronic kidney disease with secondary hyperparathyroidism and 25-OH vitamin D levels < 30 mcg/L and ages 1 month to less than 18 years. The study should be stratified by age 1 month to <2 years, 2 to <12 years, and 12 to < 18 years. This trial should not be initiated until the results of the pediatric PK/PD study (PMR 3052-1) have been submitted to and reviewed by the Agency.

Final Protocol Submission: December 2020  
Study Completion: December 2025  
Final Report Submission: June 2026

Note that the milestone due dates were adjusted due to the time that has elapsed since prior milestone due dates were negotiated.

Submit the protocols to your IND 075162, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies 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 REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosures:  
Content of Labeling: Package Insert  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEAN-MARC P GUETTIER  
06/17/2016