NDA 215559

NDA APPROVAL

Ipsen Biopharmaceuticals, Inc.
Attention: Andrew Sansone, MS
Vice President, Regulatory Affairs, Quality & Safety, North America
One Main Street, 7th Floor
Cambridge, MA 02142

Dear Andrew Sansone:

Please refer to your new drug application (NDA) dated and received March 31, 2021, which was subsequently withdrawn on August 12, 2021. We also refer to your resubmission of this NDA dated and received April 29, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sohonos (palovarotene) capsules.

We acknowledge receipt of your amendment dated February 16, 2023, which constituted a complete response to our December 23, 2022, action letter.

This NDA provides for the use of Sohonos (palovarotene) capsules for reduction in volume of new heterotopic ossification in adults and pediatric patients (aged 8 years and older for females and 10 years and older for males) with fibrodysplasia ossificans progressiva (FOP).

APPROVAL & LABELING

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 and with the minor editorial revisions listed below and reflected in the enclosed labeling.

- The following were updated to reflect the date of approval of this application: Initial U.S. Approval and Revised dates in the Prescribing Information, and Issued date in the Medication Guide.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling submitted on October 11, 2022, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215559**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for palovarotene capsules shall be 36 months from the date of manufacture when stored at 20°C to 25°C.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 215559. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

    - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),

    - the estimated demand in the U.S. for the product, and

    - the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risks of carcinogenicity, increased flare-up episodes, alterations in growth, and bone fractures, with long term use of palovarotene.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4474-1 Conduct a carcinogenicity study in rats to assess the carcinogenic potential from long-term oral exposure to palovarotene.

The timetable you submitted on July 24, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2024
Final Protocol Submission: 08/2024
Study Completion: 10/2026
Final Report Submission: 10/2027

4474-2 Conduct a carcinogenicity study in mice to assess the carcinogenic potential from long-term oral exposure to palovarotene.

The timetable you submitted on July 24, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2025
Final Protocol Submission: 08/2025
Study Completion: 04/2026
Final Report Submission: 03/2027

4474-3 Conduct a prospective observational registry study with safety objectives of comparing palovarotene exposed and unexposed patients with fibrodysplasia ossificans progressiva (FOP). Evaluate risks of increased flare-up episodes, alterations in growth, and bone fractures. The registry should also collect information on women exposed to palovarotene during pregnancy to assess for adverse events related to pregnancy through the first year postpartum, and birth and developmental outcomes through the infant's first year of life. Begin safety data collection within 90 days of protocol agreement. After protocol finalization, the PMR progress report should be submitted annually as part of the NDA annual report that also includes an evaluation of the effectiveness of meeting the registry study's safety objectives. Collect 10-year safety data from a minimum of 100 subjects, approximately half of whom will be pediatric patients (8 years to less than 18 years of age for girls and 10 years to less than 18 years of age for boys), and approximately two-thirds of whom will be exposed to palovarotene.

The timetable you submitted on August 8, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2024
Final Protocol Submission: 01/2025
Study Completion: 01/2036
Final Report Submission: 01/2037

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased palovarotene exposures in patients with moderate-to-severe hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4474-4 Conduct a clinical trial to evaluate the impact of hepatic impairment on the pharmacokinetics of palovarotene in subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment relative to healthy adult subjects with normal hepatic function, in accordance with the study design described in guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. Submit the subject-level datasets with the final report.

The timetable you submitted on July 24, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	01/2024
Final Protocol Submission:	08/2024
Trial Completion:	09/2026
Final Report Submission:	06/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocols to your IND 120181 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

REQUESTED PHARMACOVIGILANCE/ENHANCED PHARMACOVIGILANCE

We request that you submit all reports of confirmed or possible pregnancy that occur during palovarotene exposure as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the 10th year following initial U.S. approval.

We request that you provide a separate narrative summary and analysis of reports of confirmed or possible pregnancy exposure apart from your required analysis of 15-day "Alert reports," in each required postmarketing periodic safety report [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 10th year following initial U.S. approval. Your narrative summary and analyses should include interval and cumulative assessment of the reports of confirmed or possible pregnancy exposure and should provide an assessment of case details (e.g., reason for contraceptive failure, duration of contraceptive methods, duration of palovarotene therapy, information regarding maternal palovarotene continuation or discontinuation as related to gestational age of the fetus). Also provide maternal and fetal outcome(s).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[8].

If you have any questions, call Noreen Cabellon, Regulatory Project Manager, at 301-796-2899.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[8] https://www.uspnf.com/

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
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