NDA 218860

ACCELERATED APPROVAL

Ipsen Biopharmaceuticals, Inc.
Attention: Shannon Mee
Senior Director, Global Regulatory Affairs
One Main Street, 7th Floor
Cambridge, MA 02142

Dear Shannon Mee:

Please refer to your new drug application (NDA) dated and received on October 10, 2023, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Iqirvo (elafibranor) tablets.

This NDA provides for the use of Iqirvo (elafibranor) tablets for the treatment of primary biliary cholangitis (PBC), in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

APPROVAL & LABELING

1. We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

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). 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 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218860**." 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 Iqirvo (elafibranor) tablets, 80 mg shall be 24 months from the date of manufacture when stored at 15°C to 30°C (59°F to 86°F).

ADVISORY COMMITTEE

Your application for Iqirvo was not referred to an FDA advisory committee because there were no issues that warranted an advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510, you are required to conduct further an adequate and well-controlled clinical trial intended to verify and describe clinical benefit. You are required to conduct this clinical trial with due diligence. If the required postmarketing clinical trial fails to verify clinical benefit or is not

[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.

conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 7, 2024. This requirement is listed below.

4629-1 Complete Trial CLIN-60190-454, a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of elafibranor in adults with primary biliary cholangitis (PBC). Efficacy must be demonstrated using a composite endpoint of all-cause mortality, liver transplant, hepatic decompensation, change in MELD 3.0 to ≥15 in subjects with baseline MELD ≤12, and development of hepatocellular carcinoma.

The timetable you submitted on June 7, 2024, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	04/2024 (submitted)
Completion of Trial Enrollment:	05/2026
Trial Completion:	05/2029
Final trial Report Submission:	05/2030

Submit clinical protocols to your IND 162726 for this product. 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.

You must submit status reports of the progress of the clinical trial required under section 506(c) (listed above) to the NDA 180 days after the date of approval of this NDA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application’s ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a) and the following information:

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

- Number of activated trial sites
- Number of subjects screened and randomized
- Strategies for continued recruitment and retention of subjects
- Number of events accrued (i.e., blinded events pooled across treatment arms)

FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**NDA 218860 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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 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 identify the following unexpected serious risks:

[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

- adverse maternal and fetal outcomes in women and their offspring exposed to elafibranor during pregnancy
- infant exposure to elafibranor via breast milk
- fetal exposure to elafibranor due to unplanned pregnancy as a result of the potential failure of hormonal contraceptives when used concurrently with elafibranor
- myopathy due to the potential increase in the systemic exposure to rosuvastatin in patients who take elafibranor and rosuvastatin together

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:

4629-2 Conduct a ten-year worldwide descriptive study that collects prospective and retrospective data in women exposed to elafibranor during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on May 31, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	09/2025
Interim Report Submission:	09/2030
Study Completion:	09/2035
Final Study Report Submission:	03/2038

4629-3 Perform a lactation study (milk and plasma) in lactating women who have received elafibranor to measure concentrations of elafibranor and its major metabolites in breast milk and maternal plasma using a validated assay.

The timetable you submitted on May 31, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Study Completion:	12/2027
Final Study Report Submission:	06/2028

4629-4 Conduct a clinical drug-drug interaction study to evaluate the effect of elafibranor on the pharmacokinetics of combined oral contraceptives.

The timetable you submitted on May 31, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Study Completion:	06/2027
Final Study Report Submission:	12/2027

4629-5 Conduct a clinical drug-drug interaction study to evaluate the effect of elafibranor on the pharmacokinetics of rosuvastatin.

The timetable you submitted on May 31, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Study Completion:	06/2027
Final Study Report Submission:	12/2027

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.[1]

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4629-6 Conduct an in vitro phenotyping study (or studies) to assess the contribution of cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes to the metabolism of GFT1007. The findings from in vitro studies should be followed up with in vivo drug-drug interaction studies if warranted.

The timetable you submitted on May 31, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2024
Final Protocol Submission:	03/2025
Study Completion:	09/2025
Final Study Report Submission:	03/2026

4629-7 Conduct a clinical drug-drug interaction study to evaluate the effect of a breast cancer resistance protein (BCRP) inhibitor on the pharmacokinetics of elafibranor and its major metabolites.

The timetable you submitted on May 31, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	06/2025
Study Completion:	06/2027
Final Study Report Submission:	12/2027

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 162726 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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]

REPORTING REQUIREMENTS

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

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 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[6].

[5] https://www.fda.gov/media/128163/download.

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

If you have any questions, contact Terry Tsui, Regulatory Project Manager at terry.tsui@fda.hhs.gov or at 240-402-1941.

Sincerely,

{See appended electronic signature page}

Nikolay Nikolov, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

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/

NIKOLAY P NIKOLOV
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