



NDA 211710

ACCELERATED APPROVAL

Loxo Oncology, Inc.
Attention: Katie Cairati, M.S.
Executive Director, Regulatory Affairs
701 Gateway Boulevard
Suite 420
South San Francisco, CA 94080

Dear Ms. Cairati:

Please refer to your New Drug Application (NDA) dated March 24, 2018, received March 26, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vitrakvi (larotrectinib) oral solution, 20 mg/mL.

This new drug application provides for the use of Vitrakvi (larotrectinib) oral solution, 20 mg/mL for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have no satisfactory alternative treatments or that have progressed following treatment.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 prescribing information, text for the patient package insert, text for Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

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 November 20, 2018, 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 211710.**” Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

Your request for a rare pediatric disease priority review voucher has been denied. You did not qualify for the voucher, because your application did not meet the requirements to be a “rare pediatric disease product application” for the following reason:

Your application is not for a drug or biological product that is for the prevention or treatment of a rare pediatric disease. See sections 529(a)(4)(A)(i) of the Federal Food, Drug & Cosmetic Act (21 U.S.C. § 360ff(a)(4)(D)). Although your drug does have rare pediatric disease designation for the disease infantile fibrosarcoma, your application is for NTRK fusion solid tumors. FDA has determined that the serious and life-threatening manifestations of NTRK fusion solid tumors do not primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.

ADVISORY COMMITTEE

Your application for Vitrakvi (larotrectinib) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues in the intended population.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. You are required to conduct such studies with due diligence. If postmarketing studies fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 19, 2018. This requirement, along with required completion dates, is listed below.

- 3541-1 Submit the final report, including datasets, from ongoing and proposed trials conducted to verify and describe the clinical benefit of larotrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and pediatric patients with solid tumors with a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion and without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment. A sufficient number of patients will be evaluated to characterize response and durability of response for each of the following tumor types: colorectal cancer, non-small cell lung cancer, central nervous system tumors, and melanoma. A minimum of 40 patients with cancers other than colorectal cancer, non-small cell lung cancer, central nervous system tumors, melanoma, soft tissue sarcoma, thyroid cancer, infantile fibrosarcoma, and salivary cancers (e.g., breast cancer, gastrointestinal stromal tumors, cholangiocarcinoma, biliary tract cancers) will also be studied. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months from the onset of response.

Draft Protocol Submission: March 2019
Final Protocol Submission: August 2019
Study/Trial Completion: August 2024
Final Report Submission: August 2025

- 3541-2 Submit the final report, including datasets, from the first 55 patients with *NTRK*-fusion solid tumors enrolled across Study LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431), to further characterize the duration of response in patients who achieved a complete or partial response to larotrectinib. All responding patients will be followed for at

least 2 years from the onset of response and duration of response will be assessed by independent central review.

Study/Trial Completion: May 2019
Final Report Submission: March 2020

Submit clinical protocols to your IND 121211 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement 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 entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, 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 the treatment of solid tumors with NTRK-fusion proteins 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 unexpected serious risks of adverse long-term effects of larotrectinib on the growth, neurological outcomes, and development of pediatric patients, assess unexpected risks of serious adverse reactions to larotrectinib in patients who require a third dosage modification of larotrectinib for toxicity, and assess a signal of the effects of a moderate CYP3A4 inhibitor on the pharmacokinetics of larotrectinib leading to excessive toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risk(s).

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

- 3541-3 Conduct a study of larotrectinib in a sufficient number of pediatric patients with *NTRK*-fusion solid tumors to evaluate the potential serious risk of adverse long-term effects of larotrectinib on the growth and development of pediatric patients. Patients will be evaluated for growth and developmental milestones using age-appropriate screening tools and undergo neurological examination at appropriate intervals (for example, every six months) until larotrectinib is discontinued or for minimum of five years, whichever occurs first. Evaluations should include a neurologic exam, developmental milestone assessment, Karnofsky/Lansky score, growth as measured by weight and height, height velocity, height standard deviation scores (SDS), age at adrenarche if applicable (males), age at menarche if applicable (females), and Tanner Stage.

The timetable you submitted on November 19, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: March 2019
Final Protocol Submission: August 2019
Study/Trial Completion: August 2027
Final Report Submission: August 2028

- 3541-4 Conduct a study of larotrectinib 100 mg orally once daily in a sufficient number of adult or pediatric patients with a body surface area of at least 1.0 m² who experienced an adverse reaction requiring a third dosage modification of larotrectinib to better characterize the tolerability of this approved dosage modification for larotrectinib. The following information will be provided for each patient: patient age and body surface area (if pediatric), adverse reactions leading to each prior dose reduction of larotrectinib, duration of treatment on prior dose levels, duration of treatment at the 100 mg orally once daily regimen, best overall response and duration of response. and tumor information collected while receiving the 100 mg orally once daily dosage regimen.

The timetable you submitted on November 19, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: March 2019
Final Protocol Submission: August 2019
Study/Trial Completion: August 2027
Final Report Submission: August 2028

- 3541-5 Conduct a physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inhibitor on the single dose

pharmacokinetics of larotrectinib to address the potential for excessive drug toxicity.

The timetable you submitted on November 13, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 2019
Study/Trial Completion: April 2019
Final Report Submission: September 2019

Submit clinical protocol(s) to your IND 121211 with a cross-reference letter to this NDA. Submit 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 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 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 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.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 3541-6 Conduct a physiologically-based pharmacokinetic modeling study to evaluate the effect of repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of larotrectinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations.

The timetable you submitted on November 13, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 2019
Study/Trial Completion: April 2019
Final Report Submission: September 2019

- 3541-7 Conduct an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of an in vitro diagnostic device that is essential to the safe and effective use of larotrectinib for patients with *NTRK* gene fusions in solid tumor specimens.

The timetable you submitted on November 19, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: July 2021

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 121211 for this product. Submit 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 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 (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

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

Alternatively, you may submit promotional materials for accelerated approval products 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>).

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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, contact Idara Udoh within two weeks of receipt of this letter.

If you have any questions, call Idara Udoh, Senior Regulatory Health Project Manager, at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Amy McKee, M.D.
Acting Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Prescribing Information
Patient Package Insert
Instructions for Use
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/

AMY E MCKEE
11/26/2018