NDA 213756'

NDA APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Elinore Mercer, Ph.D., RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Mercer:

Please refer to your new drug application (NDA) dated September 13, 2019, received September 13, 2019, and your amendments, submitted of the Federal Food, Drug, and Cosmetic Act (FDCA) for KOSELUGO (selumetinib) capsule.

This new drug application provides for the use of KOSELUGO (selumetinib) capsule for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

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.

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 Patient Package Insert, 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.

[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.

CONTAINER LABELING

Submit final printed container labeling that is identical to the enclosed container labeling as soon as it is available, but no more than 30 days after it is printed. Please submit this labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213756**." Approval of this submission by FDA is not required before the labeling is used.

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 213756. 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.

- 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]

ADVISORY COMMITTEE

Your application for KOSELUGO was not referred to an FDA advisory committee because

(1) the safety profile is acceptable for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN);

(2) evaluation of the safety data when used for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN) did not raise significant safety or efficacy issues that were unexpected for a drug of this class;

(3) the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease;

(4) outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm

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

We note that you have fulfilled the pediatric study(ies) requirement for all relevant pediatric age groups for this application.

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 a serious risk of physeal dysplasia and the effects of growth and development, and the long-term safety effects of selumetinib in pediatric patients.

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:

3806-1 Characterize and evaluate the long-term safety effects and any potential for serious adverse risks of selumetinib on the growth and development of pediatric patients. Submit the complete final report and long-term follow-up data from pediatric patients enrolled on SPRINT and ongoing or completed studies of selumetinib.

All patients must be evaluated for growth and development milestones annually for at least 7 years from initiation of selumetinib. Evaluations must include: growth as measured by weight, height, height velocity, height standard deviation scores (SDS), age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

The timetable you submitted on March 24, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	09/2025
Final Report Submission:	03/2026

3806-2 Characterize and evaluate the long-term safety effects and any potential for specific serious adverse risks of selumetinib in pediatric patients. Submit the complete final report and long-term follow-up safety data (minimum of 7 years) from pediatric patients enrolled on SPRINT and all other ongoing or completed studies of selumetinib to include an analysis of the following toxicities in pediatric patients: ocular toxicity (including but not limited to retinal pigment epithelial detachment and retinal vein occlusion), cardiac toxicity (including but not limited to ventricular dysfunction), muscle toxicity (including but not limited to rhabdomyolysis and symptomatic and asymptomatic CPK elevation), serious gastrointestinal toxicity (including but not limited to colitis, ileus, intestinal obstruction, and intestinal perforation), and serious dermatologic toxicity.

The timetable you submitted on March 24, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	09/2025
Final Report Submission:	03/2026

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the potential for lower/higher drug exposure and resultant serious drug risks when administering selumetinib with a low-fat meal.

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

3806-3 Submit the final report and datasets from a pharmacokinetic trial in pediatric patients to confirm the effect of a low-fat meal on selumetinib exposure with the marketed capsule formulation and evaluate whether administration of selumetinib with food may alleviate gastrointestinal toxicities. Confirm appropriate dosing recommendation of selumetinib with a low-fat meal that maintains efficacy with acceptable safety.

The timetable you submitted on March 17, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2020
Final Protocol Submission:	12/2020
Study Completion:	10/2022
Final Report Submission:	04/2023

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 protocol(s) to your IND 122851 with a cross-reference letter to this 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).**

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.

ENHANCED PHARMACOVIGILANCE MONITORING

For a period of 5 years from the U.S. approval date, submit all cases reported of adverse events of special interest (AESIs), including ocular toxicity events including but not limited to retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), cardiac toxicity events (including but not limited to ventricular dysfunction), muscle toxicity events (including but not limited to rhabdomyolysis), gastrointestinal

[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.

toxicity events (including but not limited to colitis, ileus, intestinal obstruction, and intestinal perforation) with serious outcomes in pediatric patients receiving KOSELUGO for the treatment of NF-1 as 15-day Alert reports [as described under 21 CFR 314.80(c)(1)], and provide detailed analyses of these AESIs reported from clinical study, and post-marketing reports in your periodic safety report [i.e., the Periodic Adverse Drug Experience Report (PADER) required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER) format]. These analyses should show cumulative data relative to the date of approval of KOSELUGO as well as relative to prior periodic safety reports. These analyses should include case narratives, with the following information in a table format: demographics, predisposing risk factors/comorbidities, signs, symptoms and relevant laboratory data leading to diagnosis, rechallenge/dechallenge information. Medical literature reviews for case reports/case series of these AESIs reported with KOSELUGO should also be provided in the periodic safety report.

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 Prescribing Information, Medication Guide, and Patient Package Insert (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 *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] For

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with 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 FDA.gov.[9]

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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 the Regulatory Project Manager for this application.

[8] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

[9] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, please call Sharon Sickafuse, Senior Regulatory Health Project Manager, at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Deputy Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
    - Prescribing Information
    - Patient Package Insert
- Container Labeling

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/

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