



NDA [208051/S-005](#) and S-006

**SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT/COMMITMENT**

Puma Biotechnology, Inc.
Attention: AnnaLisa Bentajado, MS, RAC
10880 Wilshire Boulevard, Suite # 2150
Los Angeles, CA 90024-4106

Dear Ms. Bentajado:

Please refer to your supplemental new drug applications (sNDAs) dated June 28 (S-005) and August 1 (S-006), 2019, received June 28 and August 1, 2019, respectively, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for [Nerlynx® \(neratinib maleate\) Tablets, 40 mg.](#)

These Prior Approval supplemental new drug applications provide for the following:

- Supplement 005: [A new indication for neratinib, for use in combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.](#) ✓
- Supplement 006: [Revisions to the Drug Interactions and Clinical Pharmacology sections](#) of the Prescribing Information based on the final study reports for PMR 3223-1 and PMC 3223-4.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 Patient Package Insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, 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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(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.

We are waiving the pediatric study requirement for these applications because necessary studies are impossible or highly impracticable. Breast cancer is extremely rare in pediatric patients.

FULFILLMENT OF POSTMARKETING REQUIREMENT/COMMITMENT

We also refer to your submissions dated August 1 and September 4, 2019, containing the final reports for the following postmarketing requirement and commitment listed in the [July 17, 2017 approval letter](#).

- ✓
- 3223-1 Conduct a physiologically-based pharmacokinetic modeling/simulation study to evaluate the effect of repeat doses of moderate CYP3A4 inhibitor on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of increased drug exposure and to address the

both PMR/PMC
statuses state
submitted

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>.

potential for excessive drug toxicity. If the PBPK modeling/simulation is not feasible then a clinical pharmacokinetic trial will be conducted. Submit Final Report, datasets, and labeling.

- 3223-4 Conduct a physiologically-based pharmacokinetic modeling/simulation study or a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of neratinib and its active metabolites to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Submit Final Report with datasets.

We have reviewed your submissions and conclude that the above requirement and commitment were fulfilled.

We remind you that there is a postmarketing commitment listed in the July 17, 2017 approval letter that is still open. 3223-3

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information

³ 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>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or 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*.

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, contact Clara Lee, PharmD, Regulatory Project Manager, at Clara.Lee@fda.hhs.gov or (240) 402-4809.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Supervisory Associate Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

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/

LALEH AMIRI KORDESTANI
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