NDA 208700/S-019
NDA 208700/S-023

SUPPLEMENT APPROVAL/
FULFILLMENT OF POSTMARKETING COMMITMENT

Advanced Accelerator Applications USA, Inc.
Attention: Jouliana Jean Paul, J.D.
Global Program Regulatory Director
57 E. Willow Street
Millburn, NJ 07041

Dear Ms. Paul:

Please refer to your supplemental new drug application (sNDA) dated and received August 13, 2021, and February 25, 2022, respectively, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lutathera (lutetium Lu 177 dotatate) injection.

NDA 208700/019:

This Prior Approval sNDA provides for revisions to the CLINICAL STUDIES, Progressive, Well-differentiated Advanced or Metastatic Somatostatin Receptor-Positive Midgut Carcinoid Tumors (14.1) subsection of the package insert (PI) based on the results of the final overall survival analysis of the NETTER-1 trial. Subsection 5.3 (Secondary Myleodysplastic Syndrome and Leukemia) of the WARNINGS AND PRECAUTIONS section was also updated based on the additional follow-up information provided. Minor changes were also made to other sections of labeling to enhance clarity and brevity.

NDA 208700/023:

This Prior Approval sNDA provides for the addition of Hypersensitivity Reactions (5.6) in the WARNINGS AND PRECAUTIONS section, along with corresponding updates to the DOSAGE AND ADMINISTRATION, Important Safety Instructions (2.1), Premedication and Concomitant Medications (2.3), Dosage Modifications for Adverse Reactions (2.4); ADVERSE REACTIONS (6) and Postmarketing Experience (6.2); and, PATIENT COUNSELING INFORMATION (17) sections of the PI.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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), 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.

Because none of these criteria apply to your applications, you are exempt from this requirement.

[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.

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated August 13, 2021, under NDA 208700/019, containing the final report for the following postmarketing commitment listed in the January 26, 2018, approval letter.

3326-03 Submit the final clinical report and datasets at the time of the final analysis for overall survival (OS) for Trial NETTER-1, entitled "A Multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ^{177} Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in Patients with Inoperable, Progressive, Somatostin Receptor Positive, Midgut Carcinoid Tumors", to revise product labeling with mature OS data.

We have reviewed your submission and conclude that the above commitment was fulfilled.

We remind you that there are postmarketing requirements listed in the January 26, 2018, approval letter that are still open.

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.*[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]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR

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

314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, call Emily Pak, Regulatory Health Project Manager, at 301-837-7531.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

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/

MARTHA B DONOGHUE
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