DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208700

NDA APPROVAL

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted and received April 28, 2016, and your amendments, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lutathera (lutetium Lu 177 dotatate), injection for intravenous use, 370 MBq/mL. We also refer to our December 19, 2016, action letter regarding the application.

We acknowledge receipt of your amendment dated July 26, 2017, which constituted a complete response to our December 19, 2016, action letter.

This new drug application provides for the use of Lutathera (lutetium Lu 177 dotatate) injection for intravenous use, 370 MBq/mL for the treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults.

APPROVAL

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 text.

WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information,

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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on January 22, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels 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 (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208700**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

The dating period for Lutathera shall be 72 hours post calibration, defined as (b) (4) when stored below 25 °C (77°C).

ADVISORY COMMITTEE

Your application for lutetium Lu 177 dotatate was not referred to an FDA advisory committee because there were no public health issues raised that would benefit from a public discussion or that required the expert opinions of the Committee. In addition, the safety profile of the drug is deemed acceptable for the indicated population of patients.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) 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 Federal Food, Drug, and Cosmetic Act (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 known serious risks of renal failure, myelodysplastic syndrome, and acute leukemia.

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 risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these known serious risks.

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

3326-01 Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up from an adequate number of patients enrolled in clinical trials to identify and characterize the risk of renal failure with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

The timetable you submitted on December 21, 2017, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission:	June 2018
Interim Safety Report Submission:	September 2021
Final Report Submission:	December 2025

3326-02 Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up from an adequate number of patients enrolled in clinical trials to identify and characterize the risks of myelodysplastic syndrome and acute leukemia with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

The timetable you submitted on December 21, 2017, states that you will conduct this trial according to the following schedule:

Final Analysis Plan Submission:	June 2018
Interim Safety Report Submission:	September 2021
Final Report Submission:	December 2025

Submit Safety Reports to your IND 077219 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 safety analyses required under this section. This section also requires you to periodically report to FDA on the status of any safety evaluations 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 safety analysis otherwise undertaken to investigate a safety issue. Failure to submit an annual report for safety analyses 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:

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.

The timetable you submitted on January 11, 2018, states that you will conduct this trial according to the following schedule:

Final Report Submission: May 2021

Submit clinical protocols to your IND 077219 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 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

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 PI (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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 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, call the Regulatory Project Manager for this application.

If you have any questions, call Nataliya Fesenko, Regulatory Health Project Manager, at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
01/26/2018