CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

215833Orig1s000

Trade Name:	Pluvicto injection
Generic or Proper Name:	[lutetium (177Lu) vipivotide tetraxetan]
Sponsor:	Advanced Accelerator Applications USA, Inc., A Novartis Company
Approval Date:	March 23, 2022
Indication:	Provides for the use of Pluvicto (lutetium 177Lu vipivotide tetraxetan) injection for treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

215833Orig1s000

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215833Orig1s000

APPROVAL LETTER

NDA 215833

NDA APPROVAL

Advanced Accelerator Applications USA, Inc., A Novartis Company
Attention: Christopher Jordan, MSHS, RAC
Senior Global Program Regulatory Director
8910 Purdue Road, Suite 250
Indianapolis, IN 46268

Dear Mr. Jordan:

Please refer to your new drug application (NDA) dated July 29, 2021, received July 29, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pluvicto [lutetium (^{177}Lu) vipivotide tetraxetan] injection.

This NDA provides for the use of Pluvicto (lutetium ^{177}Lu vipivotide tetraxetan) injection for treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

APPROVAL & LABELING

We have completed our review of this application. 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 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) 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on December 17, 2021, 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 *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 215833**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Pluvicto (lutetium ^{177}Lu vipivotide tetraxetan) injection shall be 120 hours (5 days) from the date of manufacture when stored below 30^0 C .

ADVISORY COMMITTEE

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

(1) the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class or in the intended population

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since prostate cancer occurs rarely in the pediatric population.

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 a known serious risk of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications; and the potential serious signals of secondary malignancies including myelodysplastic syndrome and acute myeloid leukemia; and other serious adverse reactions in patients receiving lutetium (^{177}Lu) vipivotide tetraxetan.

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 study:

4241-1 Conduct an integrated safety analysis to further characterize the long term outcome of the known serious risk of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications; the potential serious signals of secondary malignancies including myelodysplastic syndrome and acute myeloid leukemia (MDS/AML); and other serious adverse reactions in patients receiving lutetium (^{177}Lu) vipivotide tetraxetan in the VISION study and its sub-study, Trial CAAA617C12301 (NCT04720157), Trial CAAA617B12302 (NCT04689828) and other clinical trials as appropriate. Capture data prospectively in amended case report forms to include incidence, grade, date of onset and resolution of the adverse reaction, predisposing factors and outcomes, date and quantity of red cell and platelet transfusion, use of growth factors for myelosuppression, subsequent antineoplastic therapies, radiation therapy, and hospital admissions. Follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first.

The timetable you submitted on March 8, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	09/2022
Final Protocol Submission (Analysis Plan):	03/2023
Interim Report Submission #1:	09/2025
Interim Report Submission #2:	09/2028
Trial Completion:	09/2033
Final Report Submission:	03/2034

Include the datasets with the final report submission.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of toxicities in patients with moderate and severe renal impairment.

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

4241-2 Conduct a clinical trial to determine the kidney biodistribution, dosimetry, pharmacokinetics, and safety of lutetium (^{177}Lu) vipivotide tetraxetan and assess the potential for higher drug exposure and the resultant risk of increased serious toxicities in patients with moderate and severe renal impairment. Assess long-term toxicities in these patients. Follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first. Include risk mitigation strategies to reduce potential toxicities in the final report. Design and conduct the trial in accordance with FDA Guidance for Industry titled, *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing.*

The timetable you submitted on March 8, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2022
Final Protocol Submission:	03/2023
Trial Completion:	06/2026
Final Report Submission:	12/2026

Include the datasets with the final report submission.

FDA considers the term *final* to mean that the Applicant has submitted a protocol, 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.[3]

Submit clinical protocol(s) to your IND 133661 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and 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).** 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 the 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

[3] 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.

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:

4241-3 Conduct a clinical trial to evaluate the efficacy and safety of lutetium (^{177}Lu) vipivotide tetraxetan in patients with advanced/metastatic prostate cancer who have at least one lesion with PSMA expression higher than that in normal liver parenchyma on PSMA-11 PET scan and at least one lesion with PSMA expression less than or equal to uptake in normal liver, with the following size criteria in short axis: size criteria in short axis: organs >1 cm, lymph nodes >2.5 cm, bones (soft tissue component) >1 cm. Alternatively, add cohorts of these patients to ongoing trials. Include an analysis of these safety and efficacy data.

The timetable you submitted on March 8, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2022
Final Protocol Submission:	03/2023
Trial Completion:	02/2026
Final Report Submission:	08/2026

A final submitted protocol is one that 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 133661 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/subjects 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. 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.*[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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.

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

If you have any questions, contact Kelly Chiang, Regulatory Project Manager, at Kelly.Chiang@fda.hhs.gov or 301-796-5822.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
- 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/

PAUL G KLUETZ
03/23/2022 02:03:49 PM