CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215833Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 215833
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Product Expiration Dating Period: Applicant to insert proposed shelf life and storage conditions 120 hours (5 days). Store below 30 °C, do not freeze.

FDA Assessment: An expiration dating period of 120 hours (5 days) at the time of calibration is granted when stored at the proposed storage conditions (below 30°C, do not freeze).

Drug Name/Dosage Form	Lutetium (^{177}Lu) vipivotide tetraxetan, solution for injection/infusion
Strength	1000 MBq/ml (27 mCi/ml) in a single-dose vial
Route of Administration	intravenous
Indication	TRADENAME is a therapeutic agent indicated for the 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 (b) (4)
Applicant	Advanced Accelerator Applications USA, Inc.
US agent, if applicable	

[FDA will complete these sections.]

Submit Date(s)	July 29, 2021
Received Date(s)	July 29, 2021
PDUFA Goal Date	March 29, 2022
Division/Office	Division of Oncology 1/Office of Oncologic Diseases
Review Completion Date	March 14, 2022
Established Name	Lutetium Lu 177 vipivotide tetraxetan
(Proposed) Trade Name	PLUVICTO
Pharmacologic Class	Therapeutic radiopharmaceutical
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Raymond Frankewich	Paresma Patel
Drug Product	John Amartey	Danae Christodoulou
Process and Facility	Vidya Pai	Krishnakali Ghosh
Microbiology	Bernard Marasa	Julie Nemecek
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Kristine Leahy	-
Application Technical Lead	Eldon Leutzinger	-
ORA Lead	Cassandra Abellard	-
Environmental	NA	NA

(b) (4)

RELATED/SUPPORTING DOCUMENTS

DMFs:

				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	Type II		(b) (4)	Adequate	09/14/2021
	Type II			Adequate	10/29/2021
	Type III			Not Reviewed	Adequate Information in the application

(b) (4)	Type III	(b) (4)	Not Reviewed	Adequate Information in the application

Other Documents: *IND, RLD, or sister applications*
[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	215841	^{68}Ga-PSMA-11 NDA submitted simultaneously
IND	133661	^{177}Lu-PSMA-617 IND cross-reference
IND	133925	^{68}Ga-PSMA-11 IND cross-reference

CONSULTS

N/A

TABLE OF CONTENTS

Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

Report any differences in formulation, manufacturing, container closure system, presentation, etc. ***Do not include labeling differences***.

Not applicable

1. EXECUTIVE SUMMARY

RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

No issues remain from the primary reviews of Chemistry, Manufacturing and Controls (CMC) and from that standpoint Lutetium (^{177}Lu) vipivotide tetraxetan meets all applicable standards to support the identity, strength, quality and purity that it purports.

I. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The product is a single-dose vial containing 1000 MBq/mL (27 mCi/mL) of Lutetium (^{177}Lu) vipivotide tetraxetan, solution for injection/infusion. ^{177}Lu-PSMA-617 is a radioligand therapy (RLT) that targets prostate-specific membrane antigen (PSMA)-expressing prostate cancer lesions in a specific manner by exploiting cell surface proteins mainly expressed on malignant cells. Its intended use is for treatment of adult patients with PSMA-positive mCRPC who have in turn been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy (b) (4)

PSMA-617 was initially developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ), in collaboration with University Hospital Heidelberg (Kratochwil et al 2015). Following initial nonclinical development of PSMA-617, the compound was licensed to ABX GmbH in Germany. Endocyte, Inc. assumed responsibility for global development of PSMA-617 in 2017, and initiated the pivotal Phase III Study PSMA-617-01 (also known as VISION) under IND 133661. Novartis acquired AAA in January 2018 and Endocyte, Inc. in December 2018.

In NDA 215833, there are two entities (^{177}Lu-PSMA-617 and PSMA-617) listed under Drug Substance (3.2.S). That there is no confusion and proliferation of misconceptions, it is essential to understand that the Drug Substance is actually the radiolabeled entity (^{177}Lu-PSMA-617). PSMA-617 is the ligand portion of the drug substance. On radiolabeling of PSMA-617 with $^{177}LuCl_3$, ^{177}Lu-PSMA-617 ($C_{49}H_{68}{}^{177}LuN_9O_{16}$, MW 1216.06 g/mol) is produced and has the structure shown below.

(b) (4)

[redacted]

Summary of Assessments: PSMA-617

All FDA assessment is indicated in colored fonts: Executive Summary, Drug Substance, Drug Product, Environmental Assessment, labeling, Process, Facility, Biopharmaceutics, and Microbiology.

Multiple issues had been identified with PSMA-617, some of the more important ones ranging from potential degradation products in batches to the capability of the analytical HPLC methods to detecting/resolving and quantifying the degradation products. All issues identified in the assessment of PSMA-617 are **Resolved**.

Drug Product:

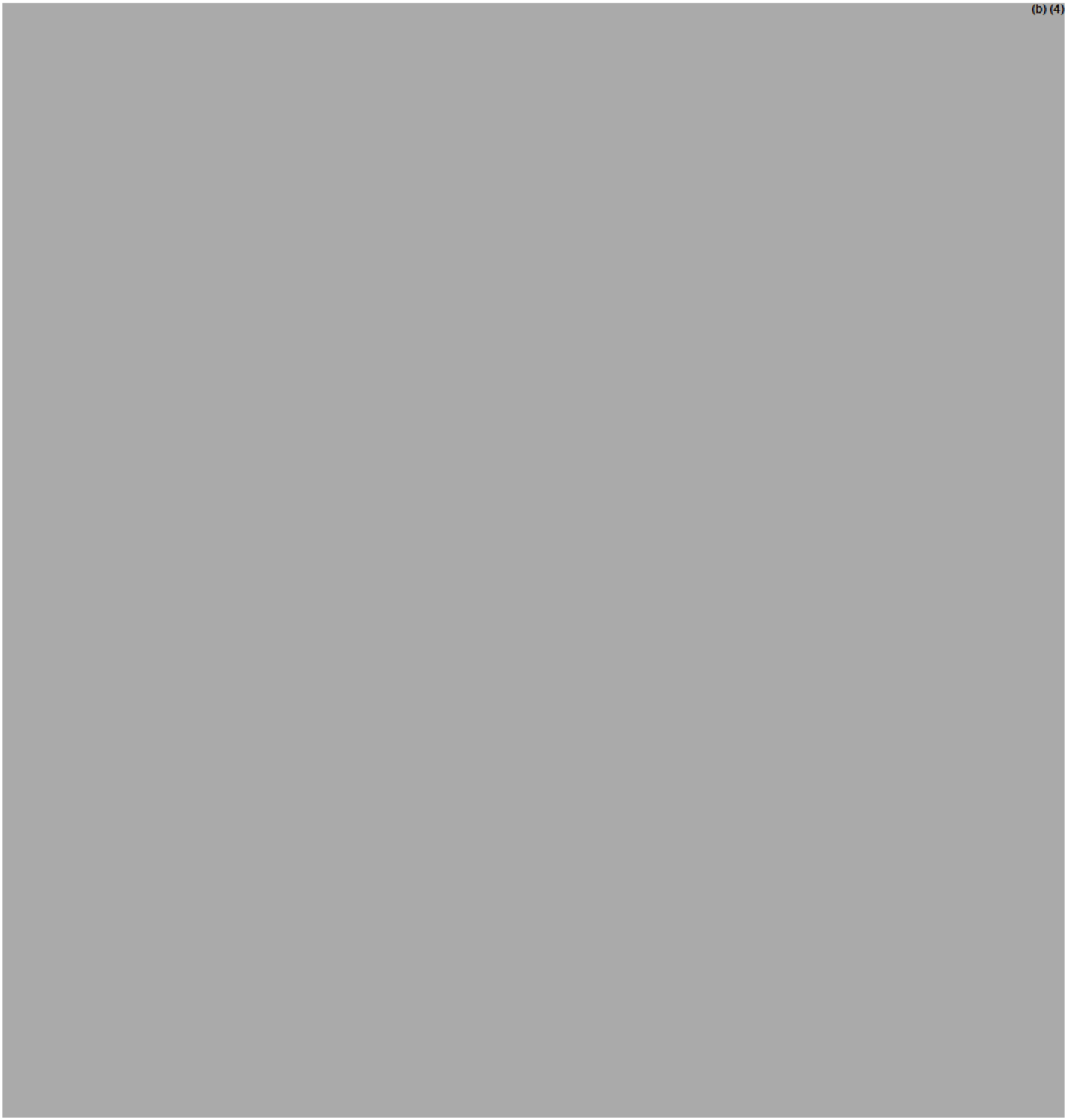
The drug product is a ready-to-use single dose vial (30 mL) containing a clear, colorless to slightly yellow colored solution of ^{177}Lu-PSMA-617 ranging from 7.5 – 12.5 mL that allows for delivery of 7.4 GBq (200 mCi) ± 10% of radioactivity at the time of administration. The vial is fitted with a (b) (4) rubber stopper and (b) (4) cap. The strength is 1000 MBq/mL at calibration time (b) (4) The shelf-life is defined as 120 hours (5 days) after calibration time; the physical half-life of ^{177}Lu is 6.65 days.

Excipients include (b) (4) (Acetic Acid and Sodium Acetate), Gentisic Acid and Ascorbic Acid (b) (4) Pentetic Acid (b) (4) and WFI (b) (4)

(b) (4)

(b) (4)

(b) (4)



Labeling:

A substantial part of the prescribing information rests in CMC and there are numerous areas ranging from Dosage Forms and strength (3) to preparation Description (11) to How Supplied/Storage and Handling (16) needing editing for clarity and sometimes for accuracy. Applicant responses have taken up several labeling meetings with numerous

edits to these sections. And in conclusion, all is acceptable, including a revised container label and carton label (received 12/17/2021) from a medications error perspective. There are no additional recommendations from the labeling reviewers.

Manufacturing:

All facilities for NDA 215833 are determined to be acceptable (email from Vidya Pai/Krishna Ghosh, 3/11/2022). See the facilities section in the Assessment Aid.

Biopharmaceutics:

Determined to be adequate (no review)

Microbiology (if applicable):

There are multiple issues for microbiology ranging from the (b) (4) (b) (4) (b) (4) The recommendation from Microbiology is adequate. See the microbiology section of the Assessment Aid.

B. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Radiochemical Identity, HPLC	•Analytical method •Reference Standard •Acceptance criterion	H, M, or L M	Applicant Resolved	Acceptable	N/A
Radiochemical purity, HPLC ITLC	•Analytical method •Reference Standard •Acceptance criterion	M	Applicant Resolved	Acceptable	N/A
Chemical purity, HPLC		L	N/A	Acceptable	N/A
	•Precursor purity	M	Applicant Resolved	Acceptable	N/A

Strength	•Purity of product Ingredients	L	N/A	Acceptable	N/A
Appearance		L	N/A	Acceptable	N/A
Particulates	•Stability •Radionuclide	L	N/A	Acceptable	N/A
Extractables	•stability	H	Applicant Resolved	Acceptable	N/A
pH	•Container/closure				
Sterility	•Formulation	H	Applicant Resolved	Acceptable	N/A
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site				
	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site				

D. List of Deficiencies; N/A

Application Technical Lead Name and Date:

Eldon E. Leutzinger, Ph.D., 3/14/2022

Life Cycle Considerations:
[FDA ATL to include any life-cycle considerations here]

2. APPLICATION BACKGROUND

^{177}Lu-PSMA-617 is a radioligand therapy (RLT) that targets prostate-specific membrane antigen (PSMA)-expressing prostate cancer lesions in a specific manner by exploiting cell surface proteins mainly expressed on malignant cells. PSMA is a promising RLT target

because it is highly expressed in PC, including mCRPC, but it has low and restricted expression in normal tissues (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). This differential expression provides a mechanism by which targeted therapeutic radiation can be delivered to cancer cells via PSMA while minimizing radiation-related side effects. PSMA-targeted RLT utilizes a radiolabeled small-molecule ligand that targets and binds with high affinity to PSMA, resulting in internalization and retention within the targeted PC cell (Ghosh and Heston 2004, Benešová et al 2015), to treat PSMA-positive mCRPC.

PSMA-617 was initially developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ), in collaboration with University Hospital Heidelberg (Kratochwil et al 2015). Following initial nonclinical development of PSMA-617, the compound was licensed to ABX GmbH in Germany.

Endocyte, Inc. assumed responsibility for global development of PSMA-617 in 2017, and initiated the pivotal Phase III Study PSMA-617-01 (also known as VISION) under IND 133661. (b) (4)

(b) (4)

On 14-Jun-2021, FDA granted Breakthrough Therapy Designation to ^{177}Lu-PSMA-617 for the treatment of adult patients with PSMA-positive mCRPC who have been treated with androgen receptor-directed therapy and taxane-based chemotherapy.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

Key interactions and CMC-specific agreements reached with FDA are listed below:

Interaction Date	Outcome
FDA Type B CMC End of Phase II, written response only Meeting under IND 133,661 20-Dec-2018	Alignment on the CMC development plan. The Agency agreed on the listed starting materials (b) (4) (b) (4) the proposed specifications for the drug substance and drug product and the proposed stability protocol.
FDA Type C Meeting, written response only Meeting under IND 133,661 24-Mar-2020	FDA agreed with the planned analytical approach to bridge the clinical trial formulations of ^{177}Lu-PSMA-617 and the commercial formulation, the planned approach for process validation at the proposed manufacturing sites, and the proposed stability plan.

The FDA's Assessment: Choose an item.

Adequate.

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

As outlined in 21CFR§25.31(b), action on a New Drug Application (NDA) is categorically excluded from the requirement to prepare an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21CFR§25.5(a), will occur if the drug is "administered at higher dosage levels, for a longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Advanced Accelerator Applications, a Novartis Company is filing a New Drug Application (NDA 215833) for the radioactive drug product lutetium (^{177}Lu) vipivotide tetraxetan injection. The active ingredient lutetium (^{177}Lu) vipivotide tetraxetan targets prostate-specific membrane antigen (PSMA), with vipivotide tetraxetan (PSMA-617) showing a high binding affinity to PSMA on prostate cancer cells. Lutetium (^{177}Lu) vipivotide tetraxetan shows specific and efficient internalization into PSMA-positive cells.

Advanced Accelerator Applications certifies that this submission of lutetium (^{177}Lu) vipivotide tetraxetan injection qualifies for categorical exclusion under 21CFR§25.31(b) as the estimated environmental intake concentration of vipivotide tetraxetan will be significantly less than 1 ppb, based on the peak production estimates within the next five years.

Furthermore, Advanced Accelerator Applications states that, to the best of its knowledge, no extraordinary circumstances exist that may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

The FDA's Assessment: ***Adequate***

The applicant claimed categorical exclusion under 21 CFR 25.31(b). The applicant provided calculation of the expected introduction concentration (EIC), based on acceptable assumptions. The value calculated was significantly less than 1 ppb and no extraordinary circumstances exist. The claim is granted.

(b) (4)

[redacted]

(b) (4)

[redacted]

10. LABELING

[FDA will complete this section.]
PLUVICTO (lutetium Lu 177 vipivotide). Vipivotide tetraxetan is also known as PSMA-617, and it is the drug substance precursor. There are no outstanding CMC-quality issues with the labeling review.

USPI
Highlights: ***Adequate***
(Add notes as necessary)

Section 2 (if relevant): Choose an item.
(Add notes as necessary)

Section 3 Dosage Forms and Strengths: ***Adequate***
(Add notes as necessary)

Section 11 Description: ***Adequate***
(Add notes as necessary)

Section 16 How Supplied/Storage and Handling: ***Adequate***
(Add notes as necessary)

Manufacturer Information (Name and Address): ***Provided: Adequate***

Carton/Container Label Choose an item.
(Add notes as necessary)
Sterility statement in carton/container label: Choose an item.
If no, explain: Click or tap here to enter text.

Radiation symbol, Radioconcentration at reference date and time after EOS, expiry after X time after EOS (referenced date and time)
Shield label Choose an item.
(As above.)

Article VI. Final Risk Assessments

[FDA will complete this section.]

INJECTABLES

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Choose an item.		Choose an item.	
Endotoxin Pyrogen	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Choose an item.		Choose an item.	
Assay (Ligand), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Choose an item.		Choose an item.	
Physical stability (Ligand)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Choose an item.		Choose an item.	
Osmolality	• Formulation	Choose an item.		Choose an item.	
pH	• Formulation • Site	Choose an item.		Choose an item.	
Particulate matter		Choose an item.		Choose an item.	
Leachables extractables	•	Choose an item.		Choose an item.	
Radiochemical Identity		Choose an item.		Choose an item.	
Radiochemical purity, HPLC		Choose an item.		Choose an item.	
Radiochemical purity, ITLC		Choose an item.		Choose an item.	
Chemical purity, HPLC		Choose an item.		Choose an item.	
Reference standard		Choose an item.		Choose an item.	
Microbial Limits	• Formulation • Raw materials	Choose an item.		Choose an item.	

	• Process parameters • Scale/equipment • Site				
Biopharmaceutics	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Choose an item.		Choose an item.	

Article VII. Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Raymond Frankewich, Ph.D. Date: January 13, 2022
Secondary Reviewer: Paresma Patel, Ph.D. Date: January 13, 2022

Drug Product: Approval

Primary Reviewer: John K. Amartey, Ph.D. Date: March 14, 2022
Secondary Reviewer: Danae Christodoulou Date: March 14, 2022

Process and Facility: Approval

Primary Reviewer: Vidya Pai, Ph.D. Date: March 14, 2022
Secondary Reviewer: Krishnakali Ghosh, Ph.D. Date: March 14, 2022

~~***Biopharmaceutics:*** Choose an item.~~

~~*Primary Reviewer:* ABCD Date: mm/dd/yyyy~~
~~*Secondary Reviewer* XYZ Date: mm/dd/yyyy~~

Microbiology: Choose an item.AApApproval

Primary Reviewer: Bernard S. Marasa, Ph.D. Date: March 14, 2022
Secondary Reviewer: Julie Nemecek, Ph.D. Date: March 14, 2022

Application Technical Lead: Approval

Eldon E Leutzinger, Ph.D. Date: March 14, 2022

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/

ELDON E LEUTZINGER
03/14/2022 04:27:18 PM

RAYMOND P FRANKEWICH
03/14/2022 08:16:59 PM

JOHN K AMARTEY
03/15/2022 05:38:23 AM

VIDYA B PAI
03/15/2022 08:05:57 AM

BERNARD S MARASA
03/15/2022 08:17:22 AM