NEW DRUG APPROVAL

Brand Name	Pluvicto™
Generic Name	lutetium Lu 177 vipivotide tetraxetan
Drug Manufacturer	Advanced Accelerator Applications USA, Inc.

New Drug Approval

FDA Approval Date: March 23, 2022

Review Designation: Priority

Review Type: Type 1 - New Molecular Entity; New Drug Application (NDA): 215833

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Prostate cancer (PC) is the most common malignant tumor in men and the second most common cause of cancer-associated mortality. In patients treated for metastatic PC the progression from a castration-sensitive to a castration-resistant stage marks the transition to the lethal phenotype of the disease [metastatic castration-resistant PC (mCRPC)]. In recent years, several new agents have been approved for treatment of mCRPC. They include androgen receptor-targeted therapies with abiraterone and enzalutamide as well as taxane-based chemotherapy with docetaxel or cabazitaxel or the bone-targeting agent radium-223-dichloride. Despite these innovations for mCRPC therapy more than 250,000 men still die of PC worldwide each year and its treatment remain challenging. Therefore, the development of novel therapeutic regimens exhibiting both effective antitumor activity and a tolerable side effect profile is warranted.

Prostate cancer (PCa) is the leading non-cutaneous malignancy among adult males in United States. It accounts for about 20% of the newly diagnosed cancers amongst U.S. men each year.

Prostate specific membrane antigen (PSMA) is a 100-kD type 2 integral transmembrane metalloenzyme/glycoprotein that has emerged as a key target in the diagnosis and treatment of metastatic castration-resistant PCa.

Efficacy

The efficacy of Pluvicto™ was evaluated in VISION (NCT03511664), a randomized (2:1), multicentre, open-label trial that evaluated Pluvicto™ plus BSoC (N = 551) or BSoC alone (N = 280) in men with progressive, PSMA-positive mCRPC. Randomization was stratified by baseline lactase dehydrogenase (LDH), presence of liver metastases, ECOG PS score and inclusion of an AR pathway inhibitor as part of BSoC at the time of randomization. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were required to have received at least one AR pathway inhibitor, and 1 or 2 prior taxane-based chemotherapy regimens. Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded if any lesions exceeding size criteria in short axis [organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm] had uptake less than or equal to uptake in normal liver. Patients received Pluvicto™ 7.4 GBq (200 mCi) every 6 weeks for up to a total of 6 doses plus BSoC or BSoC alone. BSoC administered at the investigator's discretion included ketoconazole; radiation therapy to localized prostate cancer targets; bone-targeted agents; androgen-reducing agents; AR pathway inhibitors. Patients

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

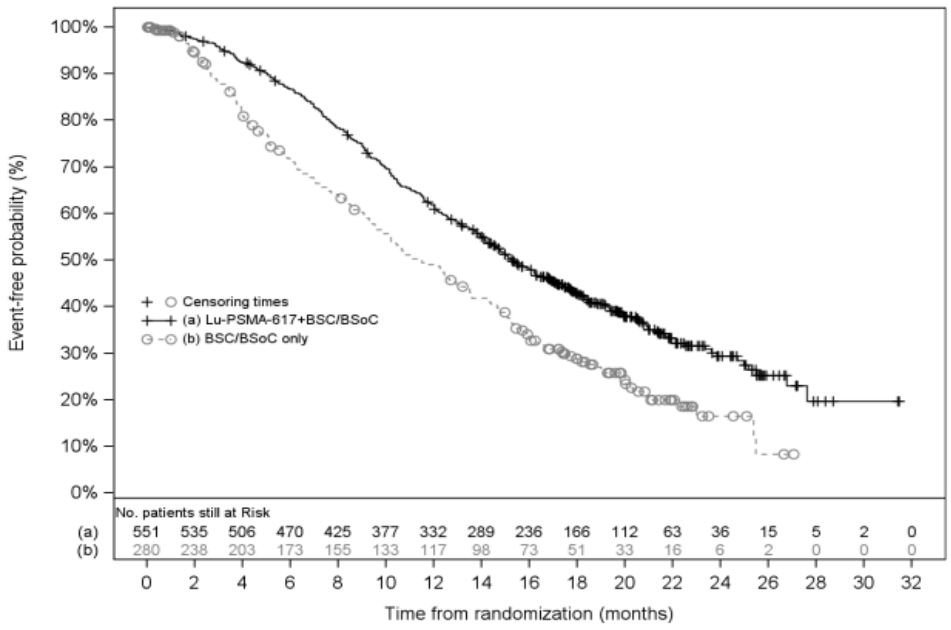
continued treatment for up to 4-6 doses, or until disease progression or unacceptable toxicity. Patients with stable disease or partial response after 4 doses of Pluvicto™ plus BSoC received up to 2 additional doses per investigator's discretion. The following patient demographics and baseline disease characteristics were balanced between the arms. The median age was 71 years (range, 40 to 94 years); 87% White; 7% Black or African American; 2.4% Asian; 92% had ECOG PS0-1; 8% had ECOG PS2. All patients had received at least one prior taxane-based chemotherapy regimen and 41% of patients received two. One prior AR pathway inhibitor had been administered to 51% of patients, 41% of patients received 2, and 8% of patients received 3 or more. During the treatment period, 53% of patients in the Pluvicto™ plus BSoC arm and 68% of patients in the BSoC alone arm received at least one AR pathway inhibitor. The major efficacy outcome measures were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per Prostate Cancer Working Group 3 (PCWG3) criteria. An additional efficacy outcome measure included was overall response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. VISION demonstrated a statistically significant improvement in both major efficacy outcome measures of OS and rPFS by BICR with Pluvicto™ plus BSoC compared to treatment with BSoC alone. Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early drop out in the control arm.

Efficacy results for VISION are presented in below Table and Figure.

	PLUVICTO Plus BSoC	BSoC
Overall Survival (OS)	N = 551	N = 280
Deaths, n (%)	343 (62%)	187 (67%)
Median, months (95% CI)[a]	15.3 (14.2, 16.9)	11.3 (9.8, 13.5)
Hazard ratio (95% CI)[b]	0.62 (0.52, 0.74)	
P-value[c]	< 0.001	
Overall Response Rate (ORR)		
Patients with evaluable disease at baseline	N = 319	N = 120
ORR (CR + PR), n (%) (95% CI)	95 (30%) (25%, 35%)	2 (2%) (0%, 6%)
Complete response (CR), n (%)	18 (6%)	0 (0%)
Partial response (PR), n (%)	77 (24%)	2 (2%)
P-value[d]	< 0.001	

[a]Based on Kaplan-Meier estimate.
[b]Hazard ratio based on the stratified Cox PH model.
[c]Stratified log-rank test two-sided p-value.
[d]Stratified Wald's Chi-square test two-sided p-value.

Figure 1. Kaplan-Meier Plot of Overall Survival in VISION



This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥ 20%) are fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. Most common laboratory abnormalities (≥ 30%) are decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

WARNINGS & PRECAUTIONS

- **Risk From Radiation Exposure:** Minimize radiation exposure during and after treatment with Pluvicto™ consistent with institutional good radiation safety practices and patient treatment procedures. Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.
- **Myelosuppression:** Perform complete blood counts. Withhold, reduce dose, or permanently discontinue Pluvicto™ and clinically treat based on severity.
- **Renal Toxicity:** Advise patients to remain well hydrated and to urinate frequently. Perform kidney function laboratory tests. Withhold, reduce dose, or permanently discontinue Pluvicto™ based on severity.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception.
- **Infertility:** Pluvicto™ may cause temporary or permanent infertility.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Lutetium Lu 177 vipivotide tetraxetan is a radioligand therapeutic agent. The active moiety of lutetium Lu 177 vipivotide tetraxetan is the radionuclide lutetium-177 which islinked to a moiety that binds to PSMA, a transmembrane protein that is expressed in prostate cancer, including mCRPC. Upon binding of lutetium Lu 177 vipivotide tetraxetan to PSMAexpressing cells, the beta-minus emission from lutetium-177 delivers radiation to PSMA-expressing cells, as well as to surrounding cells, and induces DNA damage which can lead to cell death.

Dose & Administration

ADULTS

Recommended Dosage: Administer 7.4 GBq (200 mCi) every 6 weeks for up to 6 doses.

PEDIATRICS

The safety and effectiveness of Pluvicto™ in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dose adjustment is recommended for patients with mild (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault) to moderate (CLcr 30 to 59 mL/min) renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Frequently monitor renal function and adverse reactions in patients with mild to moderate renal impairment.

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 1,000 MBq/mL (27 mCi/mL) in a single-dose vial.

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.