CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215833Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215833
PDUFA Goal Date	March 29, 2022
OSE RCM #	2021-1582
Reviewer Name	Theresa Ng, PharmD, BCPS
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	March 1, 2022
Subject	Evaluation of Need for a REMS
Established Name	^{177}Lu-PSMA-617 or (^{177}Lu) vipivotide tetraxetan
Trade Name	Pluvicto
Name of Applicant	Advanced Accelerator Applications USA, Inc. (AAA)
Therapeutic Class	Peptide receptor radionuclide
Formulation(s)	1000 MBq/ml (27mCi/ ml) in a single-dose vial for intravenous injection
Dosing Regimen	7.4 GBq (200 mCi) every 6 weeks for a total of 6 doses.

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Pluvicto (^{177}Lu-PSMA-617), a radioligand therapy targeting prostate-specific membrane antigen, is necessary to ensure the benefits outweigh its risks. Advanced Accelerator Applications USA, Inc. (AAA) submitted a New Drug Application (NDA) 215833 for Pluvicto. Initially, the Applicant's proposed indication for Pluvicto was (b) (4) (b) (4) (b) (4). The Applicant subsequently agreed to modify the indication (b) (4) (b) (4)

The risks associated with Pluvicto include myelosuppression and renal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application initially, but later agreed to include enhanced pharmacovigilance and postmarketing studies to assess the long-term risks of delayed toxicity with radiation, and enhanced pharmacovigilance to assess patients with moderate and severe renal impairment.

The Division of Risk Management (DRM) and the Division of Oncology 1 (DO1) agree that a REMS is not needed to ensure the benefits of Pluvicto outweigh its risks. The main risks of myelosuppression and renal toxicity associated with Pluvicto are due to radiation exposure and are similar to the risks associated with another radionuclide peptide receptor product containing Lutetium (^{177}Lu), Lutathera, (NDA 208700), approved in 2018 for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and does not have a REMS. The critical organs for radiation toxicity with Pluvicto are the kidney and bone marrow. The risks of myelosuppression and renal toxicity are also known risks in several of the therapies used to treat mCRPC and labeling will be utilized to communicate these risks. The risk of myelosuppression will be included in the warnings and precautions of labeling (Section 5.2) along with recommendations to perform hematology laboratory testing before and during treatment with Pluvicto. To mitigate the risk of renal toxicity, it will be included in the warnings and precautions of labeling (Section 5.3) along with instructions for the patient to remain well hydrated, urinate frequently before and after treatment, and to perform kidney function laboratory tests before and during treatment with Pluvicto.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Pluvicto (^{177}Lu-PSMA-617) is necessary to ensure the benefits outweigh its risks. Advanced Accelerator Applications USA, Inc. (AAA) submitted a New Drug Application (NDA) 215833 for Pluvicto with the proposed indication 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) (b) (4). This application is under review in the of Division of Oncology 1 (DO1). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Pluvicto (^{177}Lu-PSMA-617) is a new molecular entity[a] proposed 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). Pluvicto is a small molecule radioligand therapy (RLT) containing radionuclide lutetium (^{177} Lu) with a half-life of 42 hours linked to a moiety targeting PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon binding to PSMA-expressing cancer cells, the beta emission from Lu delivers therapeutic radiation to targeted cells as well as to surrounding cells and induces DNA damage which can lead to cell death.

Pluvicto is formulated as a single-dose vial of 1000 MBq/ml (27mCi/ ml) and the proposed dose is 7.4 GBq (200 mCi) administered intravenously (IV) every 6 weeks for a total of 6 doses[b]. Pluvicto is limited to inpatient settings to be administered by nuclear medicine physicians and staff with appropriate radiation training. Pluvicto is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 215833 relevant to this review:

- 6/14/2021: Breakthrough Therapy Designation (BTD) granted for Pluvicto.
- 7/29/2021: Sponsor submitted NDA 215833.
- 9/27/2021: Filling Communication – No Filling Review Issues Identified. Priority Review granted.
- 10/27/2021: Mid-Cycle Communication issued - No major safety concerns identified and no need for a REMS.
- 1/20/2022: In the Late-Cycle Communication the Agency requested a change in the indication (b) (4) (b) (4) (b) (4). The Agency requested changes to the indication statement from:

(b) (4)

to:

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

for the treatment of 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

In addition, the Agency asked the Applicant for plans to mitigate the risk of toxicity in patients with moderate to severe renal impairment.[1]

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Prostate cancer (PC) is the second most common cancer in men and the fifth most common cause of cancer death among men, with an estimated 1.4 million new cases and 375,304 cancer deaths in 2020 worldwide.[2] It is the second leading cause of cancer-related death among men in the United States (US), and the third leading cause in Europe.[3,4c] In the US, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020, and in Europe, the corresponding estimates were 473,344 new cases and 108,088 deaths.[5,6]

Most PCs are diagnosed in the local stage and are asymptomatic. Patients initially will undergo surgical and/or radiological therapy, along with androgen deprivation therapy (ADT). As PC progresses, most patients with metastatic disease progress to hormone insensitive state, known as metastatic castration-resistant PC (mCRPC). Ten to 20% of patients with PC become castration-resistant within 5 years and greater than 50% of them die within 3 years with historical standard therapies.[7d] The median age at diagnosis of mCRPC is 70 years and approximately 90% of these patients develop bone metastases. The expected overall survival (OS) is low (9.8 months).[8-10]

3.2 Description of Current Treatment Options

Current approved treatments for mCRPC include taxane-based chemotherapy, androgen receptor (AR) pathway inhibitors, immunotherapies, and radiopharmaceuticals. In addition, Poly (ADP-ribose) polymerase (PARP) inhibitors were recently approved in 2020 for mCRPC patients with certain germline genetic mutations.[11] The optimal sequencing of therapies is unknown and largely depends on the patient's health status, symptomology, bone health, and prior therapies.[12-14] Taxane-based chemotherapies and AR pathway inhibitors are the most commonly used agents for patients with mCRPC. However, toxicities such as bone marrow suppression, hypersensitivity, and hepatotoxicity with chemotherapeutic products, and adverse reactions due to excessive mineralocorticoid resulting in increased cardiovascular toxicity, fluid and electrolyte abnormalities with the androgen pathway inhibitors are significant risks and may limit their use. Other treatment options include bone-directed radiotherapy with radium 223, but use of this therapy is limited to those with symptomatic bone

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved*

dominant disease. As with other radiologic products, significant risk associated with radium 223 is bone marrow suppression. Immunotherapy with sipuleucel-T is only for autologous use and is associated with acute infusion reactions. PARP inhibitors are limited in those with specified homologous recombinant repair (HRR) defects or breast cancer (BRCA) gene mutations and are associated with significant risk of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML). Although none of the currently approved products for mCRPC have a REMS to mitigate their risks, many of these risks are communicated in labeling as Warnings and Precautions. There are limited options available to patients who failed taxane-based chemotherapy or for whom taxane-based chemotherapy is contraindicated or not appropriate. Hence, alternative therapeutic options are needed for patients with mCRPC. *(See Appendix 1 for summary table of FDA products approved for mCRPC.)*

4 Benefit Assessment

The efficacy and safety of Pluvicto for the treatment of PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy was demonstrated in the pivotal trial PSMA-617-01 (VISION) [NCT03511664]. Additional safety data of Pluvicto was further supported with Study PSMA-617-02 (RESIST-PC) [NCT03042312].

VISION is an international, prospective, open-label, multicenter, randomized phase 3 study of Pluvicto.[15] A total of 831 adult males with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug (NAAD) and 1 to 2 taxane-based chemotherapy regimens were randomized in a 2:1 ratio (551 investigational arm and 280 control arm) to receive either 7.4 GBq (± 10%) Pluvicto once every 6 weeks (± 1 week) for up to 4 to 6 cycles (a maximum of 6 cycles) plus best supportive care (BSC)/Best standard of care (BSoC)[e] or to BSC/BSoC only. After the 4th cycle of Pluvicto, two additional cycles could be administered for a total of 6 cycles of Pluvicto if the investigator determined response and safety criteria were met. The medium duration of exposure to randomized treatment was longer in the Pluvicto+BSC/BSoC arm (7.8 months) compared to BSC/BSoC only (2.1 months) with 47% of the patients in the investigative arm receiving 6 cycles of Pluvicto, the maximum number of cycles planned per protocol, and 68% received at least 4 cycles, the minimum recommended per protocol. The mean dose intensity was 5.5 (SD ±1.2) GBq/month, and the mean cumulative dose was 33.4 GBq (SD ±12.8). The patients in VISION were representative of the population of patients with progressive PSMA-positive mCRPC and balanced between treatment arms, though there was a slightly higher proportion of patients with ≥ 2 prior NAAD or ≥ 2 prior taxane therapy in the control arm. The majority of patients were White (87%), followed by Blacks/African Americans (7%), and Asians (2.4%). Most of the patients were over 65 years old (75.3%). Patients with severe renal impairment (GFR < 30) were excluded.

[e] Best supportive/best standard of care (BSC/BSoC) for each patient was selected and optimized at the discretion of the patient's physician prior to randomization, and was administered as per the physician's discretion and protocol at the institution. BSC/BSoC therapy was broad and included concurrent use of radiation therapy, bone-sparing agents, glucocorticoids, and AR pathway inhibitors (NAAD) in the protocol, and excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. Ra-223), or hemi-body radiotherapy treatments.

The two alternate primary endpoints based on an intention-to-treat (ITT) analysis are radiographic progression-free survival (rPFS) as assessed by blinded independent central review (BICR) and overall survival (OS). The key secondary endpoints include comparison of overall response rate (ORR), disease control rate (DCR), and time to first symptomatic skeletal event (SSE).

The Applicant reported VISION achieved statistically significant ($p < 0.001$) outcomes in its primary endpoints:

- rPFS: estimated 60% reduction in risk of radiographic disease progression or death (HR = 0.40; 99.2% CI: 0.29, 0.57) favoring Pluvicto; the median rPFS was prolonged by 5.3 months
- OS: estimated 38% risk reduction of death (HR = 0.62; 95% CI: 0.52, 0.74;) favoring Pluvicto; the median OS was prolonged by 4.0 months

Key secondary endpoints results were also statistically significant ($p < 0.001$):

- ORR: 29.8% vs. 1.7% (OR=24.99; 95% CI: 6.05, 103.24)
- DCR: 89.0% vs. 66.7% (OR=5.79; 95% CI: 3.18, 10.55)
- Time to first SSE: estimated 50% risk reduction of SSE or death (HR =0.50; 95% CI: 0.40, 0.62)

The clinical reviewer agreed that VISION demonstrated a statistically significant and clinically meaningful benefit of adding Pluvicto to BSC/BSoC in patients with mCRPC who were previously treated with a prior AR antagonist and at least one prior taxane therapy.[f] Additional sensitivity analysis conducted by the review team support the efficacy findings.

5 Risk Assessment & Safe-Use Conditions

The safety data include all subjects who received at least one dose of randomized study treatment and is based on the pivotal VISION study and a supportive study PSMA-617 (RESIST-PC), an open-label, bicentric, randomized study that evaluated two doses of Pluvicto (6.0 GBq and 7.4 GBq).[16] PSMA-617 was discontinued early due to change in sponsorship and the Applicant included safety data from 64 patients from this study in the application. The main safety analysis was conducted in VISION comprising of 529 patients who received at least 1 dose of Pluvicto and 205 patients who received at least 1 dose of BSC/BSoC. Treatment discontinuations were generally similar between both treatment arms (Pluvicto+BSC/BSoC vs BSC/BSoC only) with the exception of progressive disease (24.0% vs. 35.6%, respectively). Other causes of discontinuation include adverse events (AEs) (10.2% vs. 2.0%), no longer clinically benefiting (6.8% vs. 24.4%), and withdrew consent for treatment (4.3% vs. 18.0%).

No unexpectedly higher death rate were identified by the clinical reviewer in the Pluvicto arm compared to the control (BSC/BSoC only) arm. Eighty-five patients died while on-treatment: 66 (12.5%) patients in

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

the Pluvicto arm, and 19 (9.3%) patients in the control arm. The most frequent primary cause for death in both arms was disease progression (8.3% patients in the Pluvicto arm vs. 6.8% patients in the control arm). Fatal adverse events occurred in 2.8% in the Pluvicto arm vs 2% in the control arm. The clinical reviewer noted that some of the fatal adverse events in the Pluvicto arm such as sepsis, pancytopenia, intracranial hemorrhage, and hematoma may have been precipitated by Pluvicto's mechanism of action of affecting the bone marrow.

Higher incidences of adverse events were observed in the Pluvicto arm than the control arm. In VISION, the most common adverse reactions (≥ 20%) occurring at a higher incidence in patients who received Pluvicto compared to control arm include: fatigue (43% vs 23%), dry mouth (39% vs 0.5%), nausea (35% vs 17%), anemia (32% vs 13%), decreased appetite (21% vs 2%), and constipation (20% vs 1%). Treatment-emergent serious adverse events (TEAEs) were more frequent in the Pluvicto arm: at least 20% differences between the two treatment arms for Gastrointestinal disorders (75.4% vs. 31.7%); General disorders and administration site conditions (61.2% vs. 38.5%); and Blood and lymphatic system disorders (47.8% vs. 18.0%). The clinical reviewer concluded that the adverse events observed in VISION are consistent with the toxicities related to radiation damage to tissues that have PSMA expression, namely xerostomia (dry mouth), dry eyes, myelosuppression or hematological toxicities, nausea and vomiting, and renal effects. These toxicities are expected based on the mechanism of action of Pluvicto.[g]

Long-term follow-up safety data was planned to be collected after the end-of-study visit for a duration of 24 months or until 508 deaths (whichever occurred first). Reported AEs were similar for both the groups of patients with similar incidences of system organ class (SOC) in the two treatment arms. There were no reports of MDS/AML or other secondary malignancies. The clinical reviewer agreed with the safety findings and noted that there were no remarkable difference between the 90 day safety update (cutoff date as of June 28, 2021) and the original safety reports. However, a longer duration of follow up is required to better assess the delayed toxicities of radiation such as renal injury, pulmonary fibrosis, or secondary malignancies such as MDS/AML.

Similar to Lutathera (NDA 208700), another radionuclide peptide receptor product containing Lutetium (^{177}Lu) approved in 2018 for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), the major risks associated with Pluvicto are risks from radiation exposure, myelosuppression and renal toxicity. Pluvicto contributes to a patient's overall long-term cumulative radiation exposure and patients must follow radioprotection precautions to minimize radiation exposure to others following administration. The labeling will include information in warnings and precautions (5.1) as well as patient counseling information to advise patients to limit close contact (less than 3 feet) with household contacts for 2 days and from children and pregnant women for 7 days after treatment with Pluvicto including recommendations for separate sleeping arrangements and when

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

sexual intercourse can resume. Adverse events of special interests (AESIs) of myelosuppression and renal toxicity are further detailed below.

5.1 MYELOSUPPRESSION

The frequency of myelosuppression related events was higher in the Pluvicto+BSC/BSoC arm (47% patients) as compared to the BSC/BSoC only arm (18% patients) with anemia (32% vs 13%), thrombocytopenia (17% vs 4%, lymphopenia (14% vs 4%), and leukopenia (13% vs 2%). Of note, high grade (≥3) events of myelosuppression were higher in the Pluvicto +BSC/BSoC arm (23% patients vs 7% patients), as were the SAEs (5% patients vs 0.5% patients). Myelosuppression related events leading to withdrawal of Pluvicto were frequent (7.0% patients). The most frequent TEAEs leading to discontinuation of ^{177}Lu-PSMA-617 were myelosuppression related events (2.8% patients each with thrombocytopenia and anemia; 1.3% patients with leukopenia; 0.8% patients with neutropenia, and 0.6% patients with pancytopenia). Hematology abnormalities were more frequent with Pluvicto arm. Despite these expected hematologic abnormalities, discontinuation rate is low (< 3%). Overall, the data show that these events were manageable and often transient allowing continuation of treatment with supportive care and with only few delays in treatment cycles. The clinical reviewer maintains that myelosuppression remains a risk for this patient population and warrants careful monitoring and a readiness to delay or discontinue treatment when severely low counts are observed. Postmarket long-term study will be required to better assess this risk. Myelosuppression is expected due to the mechanism of action of Pluvicto and can be adequately communicated in labeling as a Warnings and Precautions (section 5.2) to inform prescribers to perform periodic hematology laboratory testing before and during treatment.

5.2 RENAL TOXICITY

Renal toxicity is an AESI as Pluvicto is primarily excreted through the kidney, which is also a PSMA-expressing tissue. However, renal toxicity has not been notable in both frequency and severity in the VISION study. AESIs of renal events were reported in 46 (8.7%) patients in the Pluvicto+BSC/BSoC arm, and in 12 (5.9%) patients in the BSC/BSoC only arm. The incidence of high grade ≥3 events were similar between arms (3.4% patients vs. 2.9% patients) and there were no grade 4 or 5 renal events (i.e. no events had a fatal outcome) in either arm; SAEs were reported more frequently in the BSC/BSoC arm (3.4% patients) as compared to the Pluvicto+BSC/BSoC arm (1.7% patients). More events resolved (5.5% patients) than were unresolved (3.4% patients) in the Pluvicto+BSC/BSoC arm. Despite this, the clinical reviewer determined that due to the possibility of radiotoxic damage, renal toxicity remains a risk in months to years following treatment and a longer follow-up as a postmarketing requirement is needed to better assess this risk. Pluvicto's labeling via Warnings and Precautions (section 5.3) will communicate this risk and inform prescribers that: (1) patients should be well hydrated and urinate frequently before and after administration, (2) to perform kidney function laboratory testing before and during treatment, and (3) to adjust treatment (withhold, reduce dose, or discontinue) based on severity.

6 Expected Postmarket Use

6.1 HEALTHCARE SETTING

Pluvicto is limited to inpatient settings, and is prepared and administered by nuclear medicine physicians and staff with appropriate radiation training. Like other radionuclide drugs, Pluvicto will not be marketed to the general population.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not initially propose any risk management activities for Pluvicto beyond routine pharmacovigilance and labeling consisting of warnings and precautions consistent with other radionuclides. In their response to the Late Cycle Communication, the Applicant agreed to conduct postmarketing studies to assess the delayed toxicities associated with radiation therapy, and in particular, for radiation exposure to the kidneys in patients with moderate and severe renal impairments.[17] In addition, the Applicant proposes to implement a targeted follow-up checklist for events of renal toxicity and additional pharmacovigilance measure in the investigation of renal effects in long-term follow-up in the VISION extension study.

8 Discussion of Need for a REMS

PC is the second most common cancer in men and second leading cause of cancer-related death among men in the US. Most patients with PC eventually progress to mCRPC, which remains challenging to treat. High discontinuation rates and toxicities with current treatments along with low survival rates demonstrate a need for new treatment options for the treatment of patients with mCRPC.

The Clinical Reviewer recommends approval of Pluvicto based on the efficacy and safety information from the VISION study. Both primary endpoints (rPFS and OS) and key secondary endpoints (ORR, DCR, and time to SSE) were statistically significant ($p < 0.001$) and were favorable to Pluvicto. Expected toxicities of Pluvicto were based on the mechanism of action related to radiation exposure and radiation damage to PSMA sensitive tissues and organs resulting in AEs of xerostomia (dry mouth), dry eyes, myelosuppression or hematological toxicities, nausea and vomiting, and renal effects. TEAEs reported in the VISION study such as dry mouth, nausea, diarrhea, vomiting and UTI were more frequent in the Pluvicto arm, were of low severity (Grade ≤2), and only led to permanent discontinuation of Pluvicto in ≤0.5% of patients. The risk from radiation exposure and how to minimize radiation exposure to patients, healthcare personnel, and household contacts during and after treatment with Pluvicto will be conveyed in labeling via Warnings and Precautions (section 5.1) and Patient counseling (section 17). During the LCM with the Applicant, (b) (4) agreed to revise the indication statement (b) (4) (b) (4) (b) (4). " The indication statement was modified to "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."

The critical organs for radiation toxicity of concern with Pluvicto are bone marrow and kidney. Higher incidences of myelosuppression (including anemia, thrombocytopenia, lymphopenia, leukopenia) were

reported in the Pluvicto subjects. However, despite higher frequencies of hematological abnormalities during treatment, permanent discontinuation of treatment was infrequent (< 3% in each arm), with similar incidences of hematological AEs during long-term follow-up. Prescribers should be familiar with the risk of myelosuppression as other approved therapies for mCRPC such as taxane-based chemotherapies, Radium 223, and PARP inhibitors, and another radionuclide-protein product, Lutathera, have this risk communicated in their prescribing information as a warnings and precautions. Similarly, Pluvicto will include the risk of myelosuppression in labeling (Section 5.2 Warning and Precautions) to inform prescribers to monitor patients with hematology laboratory testing closely before and during treatment.

Although renal toxicity is possible with Pluvicto, the incidence in the VISION study was not significant, with events typically of low-grade reversible serum creatinine increases. Due to potential for long-term radiation damage, the risk of renal toxicity will be included in labeling (Section 5.3 Warnings and Precautions) to inform prescribers to ensure patients are adequately hydrated, have them urinate frequently, and to perform renal function testing before and during treatment with Pluvicto. Prescribers for Pluvicto should be knowledgeable to closely monitor their patient's renal status as Lutathera and several of the therapies used to treat mCRPC (taxane-based chemotherapies and AR pathway inhibitors) have this risk listed in their warnings and precaution.

This DRM reviewer finds that a REMS is not necessary to mitigate the risks of myelosuppression and renal toxicity associated with Pluvicto as labeling is adequate to convey these risks. The Clinical reviewer for DO1 agreed with this approach. These risks are expected based on the mechanism of action of Pluvicto to PSMA-sensitive tissues and organs. Myelosuppression and renal toxicity are known risks associated with Lutathera and other therapeutics used to treat mCRPC. Prescribers treating mCRPC patients should be knowledgeable on these risks and how to monitor for them. In addition, the administration of Pluvicto would be limited to inpatient settings under the supervision of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

The Applicant agreed to conduct PMRs for more proper assessment of the risk of delayed toxicities of radiation, and in particular, to assess patients with moderate and severe renal impairments.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for Pluvicto to ensure the benefits outweigh the risks. At the time of this review, evaluation of labeling are ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 APPENDIX 1. SUMMARY OF FDA APPROVED TREATMENT FOR METASTATIC CASTRATE-RESISTANT PROSTATE CANCER

APPEARS THIS WAY ON ORIGINAL

Product Trade Name (Generic) Year of Approval	Dosing/Administration	Important Safe Use Information	Risk Management Approaches: • Boxed Warning (BW) • Warnings and Precautions (W&P)
Taxane-based Chemotherapeutics			
TAXOTERE (docetaxel) Approved in 2004	75 mg/m2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously	Should be administered when the neutrophil count is > 1500 cells/mm^3.	BW/ W&P: Toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention
JEVTANA (cabazitaxel) Approved in 2010	20 mg/m^2 administered as a one-hour intravenous infusion every three weeks in combination with oral prednisone 10 mg administered daily throughout JEVTANA treatment	For patients previously treated with a docetaxel-containing treatment	BW: Neutropenia and Hypersensitivity W&P: Bone marrow suppression, hypersensitivity, GI, urinary, and respiratory disorder, renal failure, hepatic impairment
Androgen Receptor Pathway Inhibitors or Novel Androgen Axis Drug (NAAD)			
ZYTIGA (abiraterone) Approved in 2011	1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg administered orally once daily	Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.	W&P: Hypokalemia, fluid retention, and CV adverse reactions due to mineralocorticoid excess, adrenocortical insufficiency, hepatotoxicity, and increased fractures and mortality in combination with Radium Ra 233 dichloride
XTANDI (enzalutamide) Approved in 2020	160 mg (two 80 mg tablets or four 40 mg tablets or four 40 mg capsules) administered orally once daily	Patients receiving XTANDI should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy	W&P: Seizure, posterior reversible encephalopathy syndrome (PRES), hypersensitivity, ischemic heart disease, falls and fracture
Immunotherapy			

PROVENGE (sipuleucel-T) Approved in 2010	Administer 3 doses intravenously over 60 minutes at approximately 2-week intervals Each dose of PROVENGE contains a minimum of 50 million autologous CD54+ cells activated with PAPGM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP in a sealed, patient-specific infusion bag.	Before infusion, confirm that the patient's identity matches the patient identifiers on the infusion bag Premedicate with oral acetaminophen 650 mg and an antihistamine (e.g., diphenhydramine 50 mg) ~30 minutes prior to infusion.	W&P: Intended solely for autologous use, acute infusion reactions
Radiopharmaceuticals			
XOFIGO (Radium– 223) Approved in 2013	50 kBq (1.35 microcurie) per kg body weight, given at 4 week intervals for 6 injections	For symptomatic bone metastases and no known visceral metastatic disease	W&P: Bone marrow suppression
Poly (ADP-ribose) polymerase (PARP) Inhibitors			
RUBRACA (Rucaparib) Approved in 2020	600 mg (two 300 mg tablets) taken orally twice daily, for a total daily dose of 1,200 mg	For those with deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. Patients receiving RUBRACA for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.	W&P: Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)

LYNPARZA (Olaparib) Approved in 2020	300 mg taken orally twice daily	For adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Patients receiving LYNPARZA for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.	W&P: Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), pneumonitis, venous thromboembolic events
Source: Drugs@FDA			

10.2 REFERENCES

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