CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	216023
PDUFA Goal Date	May 25, 2023
OSE TTT #	2022-1340
Reviewer Name(s)	Leah Hart, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	May 23, 2023
Subject	Evaluation of Need for a REMS
Established Name	Flotufolastat F18
Trade Name	Posluma
Name of Applicant	Blue Earth Diagnostics Ltd.
Therapeutic Class	Radiopharmaceutical
Formulation	Injection
Dosing Regimen	The recommended amount of radioactivity to be administered is 296 MBq (8 mCi), administered as an intravenous bolus injection

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Posluma (flotufolastat F18) is necessary to ensure the benefits outweigh its risks. Blue Earth Diagnostics Ltd. submitted a New Drug Application (NDA) 216023 for Posluma with the proposed indication of positron emission tomography (PET) (b) (4) of prostate-specific membrane antigen (PSMA) positive lesions in men (b) (4) (b) (4)

The Division of Imaging and Radiation Medicine (DIRM) revised the indication to positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy
- with suspected recurrence based on elevated blood prostate specific antigen (PSA) level.

The risks associated with Posluma include image misinterpretation, and radiation risk. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not necessary to ensure the benefits of Posluma outweigh its risks. The risks of imagine misinterpretation and radiation risk can be communicated and managed through labeling. The likely prescribers are familiar with the risks and the management of them, as the other approved products have similar risks. The risks are conveyed in Warnings and Precautions and Patient Counseling Information will be used to communicate the safety issues and management of toxicities associated with Posluma.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Posluma (flotufolastat F18) is necessary to ensure the benefits outweigh its risks. Blue Earth Diagnostics Ltd. submitted a New Drug Application (NDA) 216023 for Posluma with the proposed indication of positron emission tomography (PET) (b) (4) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer (b) (4) (b) (4) (b) (4) .[1]

This application is under review in the Division of Imaging and Radiation Medicine (DIRM). DIRM revised the indication to positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy

- with suspected recurrence based on elevated blood prostate specific antigen (PSA) level.

The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Posluma (flotufolastat ^{18}F), also known as fluorine-18 (^{18}F) is a new molecular entity being submitted through the 505(b)(1) pathway application.[a] Posluma is a radiohybrid (rh) prostate-specific membrane antigen (PSMA)- 7.3 (or rhPSMA-7.3 (^{18}F) SiFA-based, positron-emitting radiopharmaceutical, a radioactive diagnostic agent that binds to cells that express PSMA, including prostate cancer cells, which usually overexpress PSMA. The recommended dosage of Posluma is proposed as 296 MBq (8mCi) as an intravenous bolus injection.[b] Posluma is not currently approved in any jurisdiction.[2] Throughout the non-clinical and clinical development program, flotufolastat (^{18}F) has been referred to as ^{18}F-rhPSMA-7.3, [^{18}F] rhPSMA-7.3(^{18}F). For this review, the product will be referred to as Posluma unless otherwise indicated.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216023 relevant to this review:

- 05/25/2022: NDA 216023 submission received for Posluma with the proposed indication as a radioactive diagnostic agent indicated for positron emission tomography (PET) (b) (4) of prostate-specific membrane antigen (PSMA) positive lesions in men (b) (4) (b) (4) (b) (4)

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Prostate cancer is an adenocarcinoma as it develops primarily from the glandular part of the organ and shows typical glandular patterns on microscopic examination. The cancer cells grow and begin to multiply, initially spreading to the immediately surrounding prostate tissue and forming a tumor nodule. Prostate cancer commonly metastasizes to the bones and lymph nodes.[3]

Clinical manifestations of prostate cancer can be absent at the time of diagnosis, but late symptoms may include fatigue due to anemia, bone pain, paralysis from spinal metastases, and renal failure from bilateral ureteral obstruction.[2] Prostate cancer is among the most common cancers in males in the

[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.*

United States with an estimated 268,490 cases and 34,500 deaths annually.[4,c] In the United States, 11% of males are diagnosed with prostate cancer over their lifetime.[5] The overall five-year survival rate is over 98%.[d]

3.2. Description of Current Diagnostic Agents

PSMA is expressed in several healthy tissue including normal prostatic tissue. In most primary and metastatic prostate cancer lesions, PSMA is upregulated. The correlation between PSMA expression and Gleason grade, as well as enhanced upregulation in metastatic and castrate resistant prostate cancer, make PSMA a good target for molecular imaging. Prostate cancer-specific positron emission tomography (pcPET) has been shown to detect sites of disease recurrence at PSA levels that are lower than those levels detected by conventional imaging.

Currently there are four prostate cancer-specific PET radiotracers that have been FDA approved for the indication of identifying recurrent prostate cancer.

C-11 choline was initially approved on September 12, 2012, for the indication of PET imaging of patients with suspected prostate cancer recurrence.[6]

Fluciclovine F18 was approved on May 27, 2016, for prostate cancer patients with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment.[7]

Ga-68 PSMA was approved on December 1, 2020, for the indication of PET imaging of patients with suspected metastasis who are candidates for initial definitive therapy and with suspected recurrence based on elevated serum PSA level.[8]

Piflufolastat F 18 was approved on May 27, 2021, for the indication of PET imaging of PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy and/or with suspected recurrence based on elevated PSA levels.[9]

The serious risks associated with C-11 choline and Ga-68 PSMA are image misinterpretation and radiation exposure. The serious risks associated with fluclovine F 18 and piflufolastat F 18 include image misinterpretation, hypersensitivity reaction and radiation exposure. None of these products have a boxed warning and none of the products are approved with a REMS.

4. Benefit Assessment

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

[d] 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.*

The efficacy of Posluma was evaluated in two phase III, prospective, open label, multi-center clinical studies in men with prostate cancer: Lighthouse (BED-PSMA-301) and Spotlight (BED-PSMA-302).[1,10]

4.1. BED-PSMA-301 (Lighthouse)

Trial BED-PSMA-301 or LIGHTHOUSE was a multi-center, single-arm study that enrolled 356 patients and evaluated the detection of regional lymph node (N1) in patients with newly diagnosed unfavorable intermediate-risk, high-risk, or very high-risk PC who are candidates for radical prostatectomy (RP) with pelvic lymph node dissection (PLND). The primary objective was to assess the sensitivity and specificity of Posluma positron emission tomography (PET) in detecting N1 disease (as determined by central blinded image evaluation [BIE]) on a patient-level compared to the histopathology of lymphatic tissue removed during radical prostatectomy (RP) and pelvic lymph node dissection (PLND). Sensitivity was defined as true positive (TP)/ (TP+ false negative [FN]) and specificity as TN/ (TN + false positive [FP]). The standard of truth (SoT) comparator was histopathy from the PLND biopsy/surgery of suspected distant metastatic sites; confirmatory imaging could be used as the SoT for distant metastatic sites if histopathology was not available. The images were interpreted by three independent central PET readers who had received specific training. Three different central readers then reviewed all available conventional images and determined via consensus if Posluma PET-positive lesions identified by the central PET readers were consistent with prostate cancer.

A total of 296 patients were evaluated. The co-primary endpoint of patient-level sensitivity for detection of N1 disease ranged from 22.9% (95% confidence interval (CI): 13.7%, 34.4%) to 30.0% (95% CI: 19.6%, 42.1%) across readers, with a value of 24.3% (95% CI: 14.8%, 36.0%) for the majority read. The lower bound of the 95% CI was below the pre-specified statistical threshold of 22.5% for each of the three independent readers and for the majority read. The co-primary endpoint of patient-level specificity for detection of N1 disease ranged from 92.9% (95% CI: 88.8%, 95.9%) to 96.9% (95% CI: 93.7%, 98.7%) across the three independent central PET readers, with a value of 96.0% (95% CI: 92.6%, 98.2%) for the majority read. The study threshold was achieved by each of the three readers ($p<0.001$) with the lower bound of the 95 CI above the pre-specified statistical threshold of 82.5% for each of the three readers and for the majority read.

The secondary endpoint consisted of the verified detection rate (VDR) for distant metastases using either histopathology or confirmatory imaging as a SoT ranged from 9.9% to 14.2%. Results from a subgroup analysis demonstrates a trend towards better performance in higher risk patients. [1,6,7]

4.2. BED-PSMA-302 (Spotlight)

Trial BED-PSMA-302 or SPOTLIGHT was a prospective, phase 3, multi-center, single-arm diagnostic imaging study that enrolled 391 patients and evaluated the detection of prostate cancer (PC) lesions in men with suspected recurrence based on elevated serum PSA levels (also known as biochemical recurrence or BCR) who were being considered for curative-intent salvage treatment. The primary objective was to assess the patient-level Correct Detection Rate (CDR) and region-level positive predictive value (PPV) of Posluma PET for BCR. In the 60 days post-PET scan, patients underwent an

image-guided biopsy or confirmatory convention imaging of any PET-positive lesions as the SoT comparator. The images were interpreted by three independent central PET readers who had received specific training. Three different central readers then reviewed all available conventional images and determined via consensus if Posluma PET-positive lesions identified by the central PET readers were consistent with prostate cancer.

A total of 366 patients were evaluated (EAP) and 288 Per Protocol Population (PP). The PP population excludes patients who did not have either histopathology or serial conventional imaging to allow a longitudinal SoT assessment. The co-primary endpoint of patient level CDR in the EAP ranged from 51.4% (95% CI: 46.1%, 56.6%) to 54.1% (95% CI: 48.8%, 59.3%) across the three readers, with a value of 56.8% (95% CI: 51.6%, 62.0%) for the majority read. The lower bound of the 95% confidence interval was above the pre-specified statistical threshold of 36.5% for each of the three independent readers and the majority read. For the patient-level CDR, the threshold was achieved by each of the three readers ($p<0.0001$). Values were higher for the PP, ranging from 59.0% (95% CI: 53.1%, 64.8%) to 61.5% (95% CI: 55.6%, 67.1%) across the three independent central PET readers, with a value of 63.9% (95% CI: 58.0%, 69.4%) for the majority read. The lower bound of the 95% CI was above the pre-specified statistical threshold of 36.5% for each of the three independent central PET readers and for the majority read. Values were highest for the subpopulation of patients with histopathology available as SoT, ranging from 73.9% (95% CI: 61.9%, 83.7%) to 76.8% (95% CI: 65.1%, 86.1%) across the three independent central PET readers, with a value of 81.2% (95% CI: 69.9%, 89.6%) for the majority read with the lower bound of the 95% CI was above the pre-specified statistical threshold of 36.5%.

The co-primary endpoint of regional-level PPV for the EAP ranged from 46.2% (95% CI: 42.0%, 50.3%) to 60.3% (95% CI: 55.1%, 65.5%) across the three readers, with a value of 59.7% (95% CI: 54.7%, 64.7%) for the majority read. Although the lower bound of the 95% CI was below the pre-specified statistical threshold of 62.5% for each of the three independent central PET readers and for the majority read, higher PPV results were observed in region-level PPV for the PP with values ranging from 51.6 (95% CO: 47.1%, 56.2%) to 64.9% (95% CI: 59.5%, 74.4%) across three independent central PET readers with a value of 64.2 (95% CI 58.9%, 69.5%) for the majority read. The lower bound of the 95% CI was above 50% for two out of three of the readers as well as for the majority read. [1,6,7]

Although both BED-PSMA-301 and 302 failed to meet one of the two pre-specified endpoints, the clinical reviewer concludes that the efficacy of Posluma in the two pivotal trials reveals the clinical utility of this imaging agent in the populations investigated.[e] Please refer to DIRM's Multi-disciplinary Review and Evaluation for a detailed clinical review of efficacy. [10,11]

5. Risk Assessment & Safe-Use Conditions

[e] 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 safety of Posluma was evaluated in 6 healthy volunteers and 757 patients with prostate cancer in Phase I and Phase III clinical studies.

Serious Adverse Reactions

No serious adverse reactions were attributed to Posluma. In the prospective Phase I and Phase III clinical trials, the most frequently reported adverse reactions were diarrhea [5/747 (0.7%)], hypertension [4/747 (0.5%)], and injection site pain [3/747 (0.4%)].

Deaths

There were two deaths reported in BED-PSMA-302. One patient experienced a TEAE leading to death on Day 3, two days after Posluma administration that was considered as possibly related to the study drug by the investigator but not related to Posluma administration by the Applicant. The patient was a 73-year-old male with biochemical recurrence (BCR) of prostate cancer, hypertension, and chronic kidney disease who went for a run the morning of his death, and afterwards complained of dizziness and chest pain. He was found unresponsive later that day. Applicant disagrees with the investigator assessment on the basis that this patient had multiple risk factors for both pulmonary embolism and coronary artery disease including underlying cancer, hypertension, and chronic kidney disease. The clinical reviewer agreed that the Applicant's conclusion that this TEAE is unrelated to Posluma since the drug has no known pharmacological activity and the patient had a medical history with risk factors for sudden death from a cardiovascular event or pulmonary embolism.[10]

A second patient experienced two non-treatment-emergent AEs leading to death. The MedDRA PTs: interstitial lung disease and pulmonary fibrosis; however, neither event met the definition of a TEAE, as both events occurred on Day 15, outside of the specified time window per the definition of a TEAE. Neither event was considered to be related to rhPSMA-7.3 (^{18}F). The clinical reviewer agrees that the Applicant's determination that this death was not related to Posluma administration is reasonable given the lack of a temporal relationship and the patient's baseline lung disease.[10]

No deaths occurred in BED-PSMA-101 and BED-PSMA-301.

Like other pcPE radiotracers, Posluma includes risks of image misinterpretation, and radiation risk.

5.1. Risk of Image Misinterpretation

Labeling will note that image misinterpretation errors can occur with Posluma imaging. The Warnings and Precautions section of the label communicates that a negative image does not rule out the presence of prostate cancer and that a positive image does not confirm the presence of prostate cancer. The section warns that Posluma uptake is not specific for prostate cancer and may occur with other types of cancer. This Warning and Precaution also warns of the risk of variable interpretation in patients with suspected prostate cancer recurrence. The interpretation of the Posluma PET scan may differ depending on the image reader and the inter-reader agreement for interpretations was low. [1] The risk of image misinterpretation will be communicated in the Warnings and Precautions section of the label.

5.2. Radiation Risks

Labeling will note that Posluma use can contribute to a patient's overall long-term cumulative radiation exposure and notes that long-term cumulative radiation exposure is associated with an increased risk for cancer. Labeling instructs to ensure safe handling and preparation procedures to protect patients and healthcare workers from unintentional radiation exposure. Patients are to be advised to hydrate before and after administration and to void frequently after administration. The risk from radiation exposure will be communicated in the Warnings and Precautions section of the label, as well as via recommended dose modifications to manage radiation toxicities in the Dosage and Administration section of the label.[1] Expected Postmarket Use

According to the current proposed indication, if approved, Posluma will be administered by health care professionals with experience in managing radiolabeled products in inpatient and outpatient settings where these products are routinely handled and administered.

6. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Posluma beyond routine pharmacovigilance and labeling.

7. Discussion of Need for a REMS

The considerations for a REMS includes an evaluation of the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing and patient population.

Posluma is a radioactive diagnostic agent, with the proposed indication of positron emission tomography (PET) (b) (4) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer

- With suspected metastasis who are candidates for initial definitive therapy
- With suspected recurrence based on elevated blood prostate specific antigen (PSA) level.[1,10,11]

Prostate cancer is among the most common cancer among men in the United States. In the United States, 11% of males are diagnosed with prostate cancer over their lifetime.

The Clinical Reviewer recommends approval of Posluma based on the efficacy and safety information currently available.[1,10,11] This reviewer has determined that a REMS is not necessary to ensure the benefits of Posluma outweigh its risks. The risks associated with the use of Posluma are image misinterpretation, and radiation risk. These risks are similar to other diagnostic agents approved to detect prostate cancer (C-11 choline, Ga-68 PSMA, fluciclovine F 18 and piflufolastat F 18). None of these products have a boxed warning in its label or are approved with a REMS. The likely prescribers will most likely be knowledgeable with the diagnosis and management of the risks. Similar to other radioactive diagnostic agents, the risks of Posluma will be conveyed in the Warnings and Precautions in

the labeling which will be used to communicate the safety concerns and management of those safety concerns, as will information in Patient Counseling Information.

8. Conclusion & Recommendations

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

Should DIRM have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

9. Appendices

9.1. References

[1] Draft Prescribing Information for Posluma as currently edited by the FDA, last updated May 17, 2023.

[2] Blue Earth Diagnostics Ltd. Summary of Clinical Safety for Posluma, dated May 25, 2022.

[3] Leslie SW, Soon-Sutton TL, R I A, et al. Prostate Cancer. [Updated 2023 Mar 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470550/

[4] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et. al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524.

[5] https://seer.cancer.gov/statfacts/html/prost.html (Accessed on February 16, 2023)

[6] Choline C 11. Prescribing Information (last updated 11/2013).

[7] Axumin. Prescribing Information (last updated 8/2020).

[8] Gallium Ga 68 PSMA-11. Prescribing Information (last updated 12/2020).

[9] Pylarify. Prescribing Information (last updated 05/2021).

[10] Multi-disciplinary Review and Evaluation: NDA 216023 Posluma (flotufolastat F 18), injection. Review in progress; accessed May 23, 2023.

[11] Alice Cheuk. Clinical Review Presentation. Mid-Cycle Meeting, dated October 21, 2022.

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