POSLUMA® (flotufolastat F 18) injection

INDICATION

POSLUMA® (flotufolastat F 18) injection is indicated for positron emission tomography (PET) 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 serum prostate-specific antigen (PSA) level

IMPORTANT SAFETY INFORMATION

- Image interpretation errors can occur with POSLUMA PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of POSLUMA for imaging metastatic pelvic lymph nodes in patients prior to initial definitive therapy seems to be affected by serum PSA levels and risk grouping. The performance of POSLUMA for imaging patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels. Flotufolastat F 18 uptake is not specific for prostate cancer and may occur in other types of cancer, in non-malignant processes, and in normal tissues. Clinical correlation, which may include histopathological evaluation, is recommended.
- Risk of Image Misinterpretation in Patients with Suspected Prostate Cancer Recurrence: The interpretation of POSLUMA PET may differ depending on imaging readers, particularly in the prostate/prostate bed region. Because of the associated risk of false positive interpretation, consider multidisciplinary consultation and histopathological confirmation when clinical decision-making hinges on flotufolastat F 18 uptake only in the prostate/prostate bed region or only on uptake interpreted as borderline.
- POSLUMA use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Advise patients to hydrate before and after administration and to void frequently after administration. Ensure safe handling to minimize radiation exposure to the patient and health care providers.
- The adverse reactions reported in ≥0.4% of patients in clinical studies were diarrhea, blood pressure increase and injection site pain.
- Drug Interactions: androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, may result in changes in

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uptake of flotufolastat F 18 in prostate cancer. The effect of these therapies on performance of POSLUMA PET has not been established.

To report suspected adverse reactions to POSLUMA, call 1-844-POSLUMA (1-844-767-5862) or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Full POSLUMA prescribing information is available at www.posluma.com/prescribing-information.pdf

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POSLUMA® (flotufolastat F 18) injection

POSLUMA Scientific and Clinical Background

BACKGROUND

POSLUMA® (generic name: flotufolastat F 18) injection, formerly known as rhPSMA-7.3 (18F)), is a diagnostic, micro-dose radiopharmaceutical designed to bind to the extracellular epitope of the PSMA extracellular protein, which is overexpressed in prostate cancer. POSLUMA was approved by the FDA on May 25th 2023. The approved indication is:

POSLUMA® (flotufolastat F 18) injection is indicated for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with

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

rhPSMA compounds consist of a radiohybrid ("rh") Prostate-Specific Membrane Antigen-targeted receptor ligand which attaches to and is internalized by prostate cancer cells and they may be radiolabeled with ^{18}F for PET imaging, or with isotopes such as ^{177}Lu or ^{225}Ac for therapeutic use – providing the potential for creating a true theranostic technology. They may play an important role in patient management in the future, and offer the potential for precision medicine for men with prostate cancer. Radiohybrid technology and rhPSMA originated from the Technical University of Munich, Germany. Blue Earth Diagnostics acquired exclusive, worldwide rights to rhPSMA diagnostic imaging technology Therapeutics which is investigational at this time from Scintomics GmbH in 2018, and therapeutic rights in 2020, and has sublicensed the therapeutic application to its sister company Blue Earth Therapeutics.

Blue Earth Diagnostics has completed two Phase 3 clinical studies evaluating the safety and diagnostic performance of ^{18}F-rhPSMA-7.3 PET imaging in prostate cancer: ("SPOTLIGHT," NCT04186845), in men with recurrent disease and ("LIGHTHOUSE," NCT04186819), in men with newly diagnosed prostate cancer.

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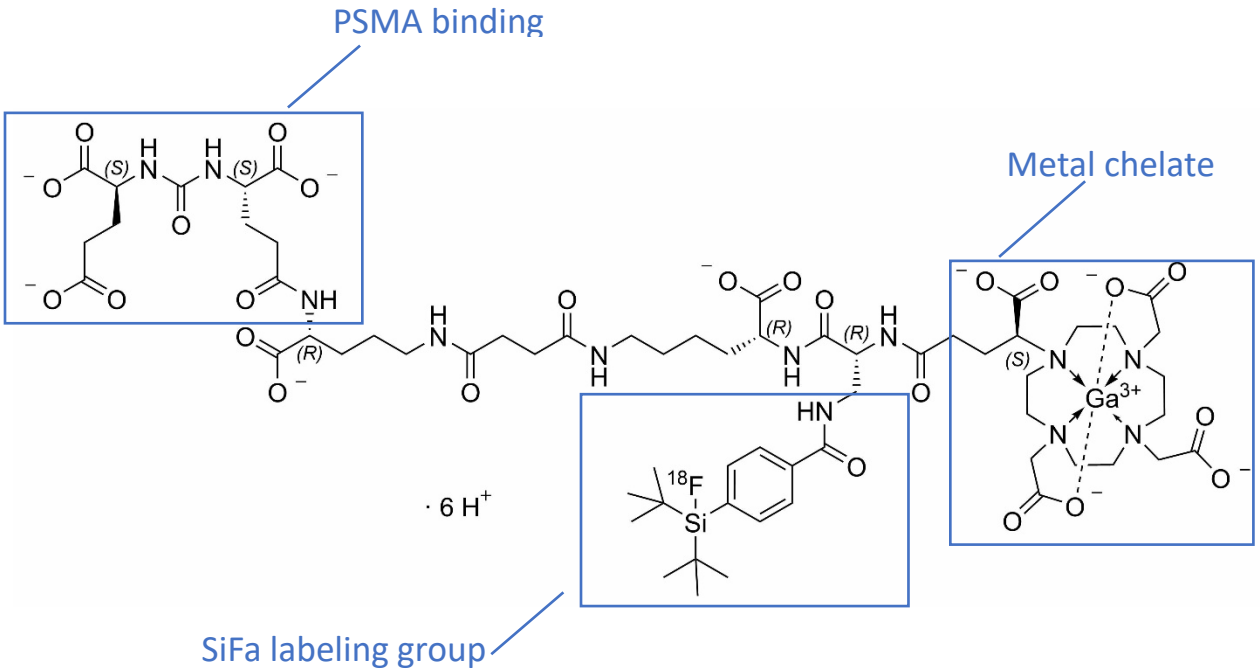
CHEMICAL COMPOSITION

The molecular structure of ^{18}F-RHPSMA-7.3 is shown below in figure 1. The molecular weight is 1537.3 g/mol.



PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA)

PSMA is a 750-amino acid type II transmembrane glycoprotein located on cell surfaces that is significantly increased (100- to 1000-fold) in prostate cancer cells (Troyer et al., 1995; Silver et al., 1997; Bostwick et al., 1998; Ghosh and Heston, 2004; Mannweiler et al., 2009) and it is reported that only 5% to 10% of primary prostate cancer tumors or metastatic lesions are PSMA expression-negative (Budäus et al., 2016; Maurer et al., 2016). The significant over expression of PSMA in most prostate cancer cells makes it an excellent target for imaging in prostate cancer.

MECHANISM OF ACTION

^{18}F-rhPSMA-7.3 binds to and is internalized by cells that express PSMA, including prostate cancer cells, which usually overexpress PSMA. Fluorine-18 is a ß+ emitting radionuclide that can be detected using positron emission tomography.

BIODISTRIBUTION

After intravenous administration, flotufolastat F 18 distributes to the liver (15.8% of administered activity), heart blood pool (7.4%), and kidneys (3.2%), it is cleared from the blood.

Elimination is by urinary excretion. Approximately 7% of the administered activity was excreted in the urine in the first 2 hours post-injection with approximately 15% excreted by 4.5 hours post-injection.

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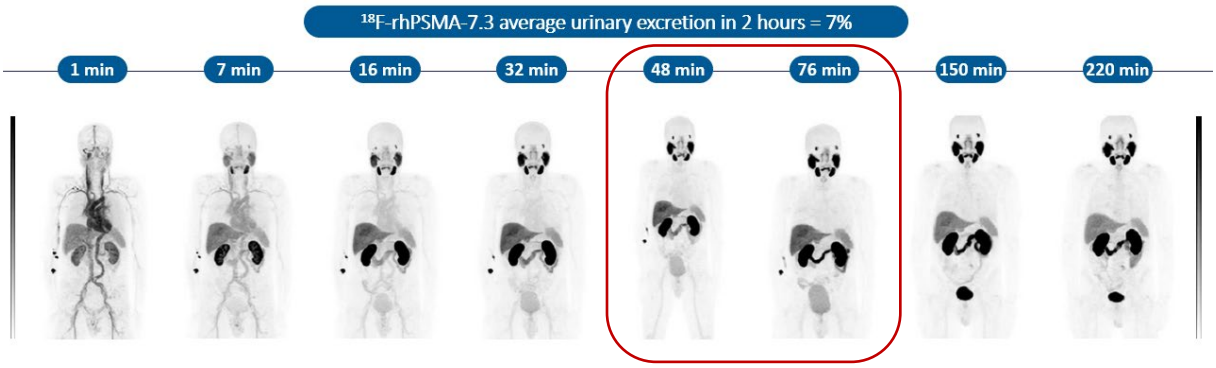

Reference: Toivanen T, et al. J Nucl Med. 2021;62(5):679–684.

DOSING, ADMINISTRATION, IMAGE ACQUISITION, IMAGE INTERPRETATION

Patients should be adequately hydrated prior to administration of POSLUMA and to continue drinking and voiding frequently for the first few hours following administration to reduce radiation exposure.

The recommended amount of radioactivity to be administered is 296 MBq (8 mCi) as an intravenous bolus injection. After the POSLUMA, an intravenous flush of sterile 0.9% Sodium Chloride Injection, USP is administered to ensure full delivery of the dose. Patients are encouraged to void immediately prior to the scan.

Patients are positioned supine with arms above the head. The recommended start time for image acquisition is approximately 60 minutes after POSLUMA injection. It is recommended that image acquisition should start from mid-thigh and proceed to the base of the skull. Scan duration is approximately 20 minutes depending on the number of bed positions and acquisition time per bed position (typically 3 minutes). Adapt imaging technique according to the equipment used and patient characteristics in order to obtain the best image quality possible

Localization of PSMA-positive lesions consistent with cancer is based on POSLUMA uptake compared to physiologic activity in background tissue. Focal increased uptake of POSLUMA may represent metastatic disease. Patterns of physiologic uptake and the available clinical history should be considered during the interpretation of POSLUMA images.

PHARMACODYNAMICS

The relationship between flotufolastat F 18 plasma concentrations and image interpretation has not been studied. Flotufolastat F 18 is a micro-dose (≤ 100 micrograms) radiopharmaceutical with no known pharmacologic effects.

CLINICAL EXPERIENCE – INITIAL DIAGNOSIS AND BIOCHEMICAL RECURRENCE OF PROSTATE CANCER

The efficacy and safety of POSLUMA was evaluated in two studies, LIGHTHOUSE, and SPOTLIGHT, in men with both initial diagnosis of prostate cancer and those with suspected disease recurrence based on

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elevated PSA levels. For both studies, POSLUMA scans were initially read by on site readers and subsequently by blinded, central readers for the efficacy analysis.

LIGHTHOUSE evaluated POSLUMA (flotufolastat F 18) injection PET scans in 356 men with newly diagnosed prostate cancer who were eligible for and already scheduled for radical prostatectomy with pelvic lymph node dissection (RP+PLND) as definitive therapy. Sensitivity and specificity for detection of pelvic lymph node metastasis was assessed using pelvic lymphatic tissue removed during RP+PLND (and assessed by microscopic analysis) as the standard of truth (SoT); detections of distant metastatic disease (M1) were also assessed.

Clinical Summary: In the 296 patients who proceeded with surgery, sensitivity for detecting pelvic lymph node (N1) cancer spread was shown to be 23% to 30% across the three blinded readers, and specificity was 93% to 97%. There were numerical trends towards higher sensitivity among patients with PSA greater than or equal to the median value (8.4 ng/mL) and among patients with high-risk or very high-risk categorization. As a percentage of the 352 patients with an evaluable POSLUMA scan, 10% (95% CI: 7% to 13%) had at least one matching positive distant metastatic (M1) lesion between the POSLUMA

majority read and a reference standard consisting of other imaging evaluated by a separate consensus panel or histopathology.

Overall performance of POSLUMA PET for detecting spread of cancer to regional lymph nodes in patients with newly diagnosed prostate cancer.

N=296	Reader 1	Reader 2	Reader 3
True Positive	21	19	16
False Positive	16	14	7
True Negative	210	212	219
False Negative	49	51	54
Sensitivity, (%) [95% CI]	30% [20, 42]	27% [17, 39]	23% [14, 35]
Specificity, (%) [95% CI]	93% [89, 96]	94% [90, 97]	97% [94, 99]
Positive Predictive Value, (%) [95% CI]	57% [40, 73]	58% [39, 75]	70% [47, 87]
Negative Predictive Value, (%) [95% CI]	81% [76, 86]	81% [75, 85]	80% [75, 85]

Source: FDA approved drug label.

In SPOTLIGHT, POSLUMA (flotufolastat F 18) injection PET scans were evaluated in 389 men previously treated with definitive therapy who were suspected to have prostate cancer recurrence based on elevated PSA level. Endpoints assessed included the overall detection rate/percent positivity and patient level positive predictive value (PPV). PPV was defined as true positive patients (as assessed by standard of truth) divided by all PET positive patients (true positives/true positives + false positives).

Clinical Summary: The average detection rate (n=389) was shown to be 83%. In patients with histopathology available for SoT assessment, the PPV was shown to be 82%.

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Patient-Level POSLUMA PET results and percent PET positivity stratified by serum PSA level in SPOTLIGHT by majority read (N=389).

PSA (ng/mL)	N	PET Positive Patients					PET Negative Patients	Percent PET Positivity [95% CI]
		Total	Histopathology		Imaging only[a]			
			PA	NPA	PA	NPA		
< 0.5	121	77	6	4	27	40	44	64% [54,72]
≥ 0.5 and < 1	67	51	7	3	24	17	16	76% [64,86]
≥ 1 and < 2	45	42	10	2	18	12	3	93% [82, 99]
≥ 2	156	152	33	3	84	32	4	97% [94, 99]
Total	389	322	56	12	153	101	67	83% [79, 86]

PSA = prostate-specific antigen, PA = positive agreement, NPA = no positive agreement, CI = confidence interval,
[a]Imaging comprised of one or more of the following: CT, MRI, ^{99m}Tc Bone Scan, fluciclovine F 18 PET.
Source: FDA approved drug label.

USER TRAINING

All POSLUMA users will be offered product training by a program provided by Blue Earth Diagnostics, Inc. The training will include:

- Imaging and Interpretation Manual
    - Including the POSLUMA Prescribing Information (USPI) and detailed background and supportive data describing image acquisition and interpretation techniques

- Image Acquisition Training
    - Blue Earth Medical Affairs training via live or virtual presentation

- Image Interpretation Training
    - Self-directed training for imaging physicians
        - Includes video of expert reader describing and reporting POSLUMA cases

Disclaimer: The POSLUMA Image Acquisition Training is provided to help familiarize imagers with techniques for the safe and effective use of POSLUMA. The responsibility for the accurate and timely acquisition and interpretation of images using POSLUMA PET/CT scanning rests with the nuclear medicine physician or radiologist supervising the PET/CT imaging facility. The POSLUMA Image Acquisition Training is not intended to substitute for the independent medical judgement of the physician(s) responsible for the individual patient's management, nor is it a guarantee of any specific clinical results.

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POSLUMA SAFETY PROFILE

The safety of POSLUMA was evaluated in 747 patients with prostate cancer. The adverse reactions reported in ≥0.4% of patients in clinical studies were diarrhea, blood pressure increase, and injection site pain.

There are no contraindications to the use of POSLUMA. Please see page one for Important Safety Information.

CONCLUSION/SUMMARY

POSLUMA® (generic name: (Flotufolastat F 18) injection, formerly known as rhPSMA-7.3 (18F)), is a diagnostic radiopharmaceutical designed to bind to the extracellular epitope of the PSMA extracellular protein, which is usually overexpressed in prostate cancer. POSLUMA was approved by the FDA on May 25th, 2023, with the following indication:

> POSLUMA injection is indicated for positron emission tomography (PET) imaging of prostate specific membrane antigen (PSMA) positive lesions in men with
>
> - with suspected metastasis who are candidates for initial definitive therapy
> - suspected prostate cancer recurrence based on elevated blood PSA level

POSLUMA binds to the extracellular epitope of the PSMA extracellular protein, which is usually overexpressed in prostate cancer, and is thus an ideal imaging target. After intravenous administration, the highest amounts of flotufolastat (F 18) are found in liver, heart blood pool, and kidneys; it is cleared from the blood rapidly via urinary excretion.

The imaging protocol and interpretation criteria are described herein as well as in the Prescribing Information (see “Dosing, Administration, Image Acquisition, Image interpretation”, above). All

POSLUMA customers will be offered product training by a program provided by Blue Earth Diagnostics, Inc. This will include information on image acquisition and interpretation principles, image acquisition logistics, as well as image interpretation methodology.

The efficacy and safety of POSLUMA were evaluated in two studies, one each in men with newly diagnosed prostate cancer and biochemical recurrence. The results are described above in “Clinical experience – Initial Diagnosis and Biochemical Recurrence of Prostate Cancer”.

The POSLUMA clinical database consists of 763 subjects. There are no contraindications to the use of POSLUMA. Please see page one of this document for important safety information.

Further medical information about POSLUMA can be obtained by calling 1-844-POSLUMA. Full prescribing information is available at: **www.posluma.com/prescribing-information.pdf**

To report suspected adverse reactions to POSLUMA, call 1-844-POSLUMA (1-844-767-5862) or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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