

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212642Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

*****Pre-decisional Agency Information*****

Memorandum

Date: August 7, 2020

To: Shane Masters, M.D.
Division of Imaging and Radiation Medicine (DIRM)

Diane Hanner, Regulatory Project Manager, DIRM

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Gallium Ga 68 PSMA-11 Injection, for intravenous use

NDA: 212642

In response to DIRM's consult request dated October 15, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Gallium Ga 68 PSMA-11 Injection.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DIRM on August 4, 2020, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 18, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

11 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 26, 2020

Requesting Office or Division: Division of Medical Imaging and Radiation Medicine (DMIRM)

Application Type and Number: NDA 212642

Product Name and Strength: Ga 68 PSMA-11 Injection, 18.5 MBq/mL to 185 MBq/mL (0.5 mCi/mL to 5 mCi/mL)

Applicant/Sponsor Name: University of California, Los Angeles

OSE RCM #: 2019-1879-1

DMEPA Safety Evaluator: Devin Kane, PharmD

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

University of California, Los Angeles submitted a revised container label received on May 18, 2020 for Ga 68 PSMA-11 NDA 212642. The revisions are in response to recommendations that we made during a previous label and labeling review.^a We reviewed the revised container label for Ga 68 PSMA-11 to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Kane, D. Label and Labeling Review for Ga 68 PSMA-11 (NDA 212642). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 02. RCM No.: 2019-1879.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 18, 2020

- **Container Label**



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/s/

DEVIN R KANE
05/26/2020 08:15:49 AM

HINA S MEHTA
05/26/2020 09:02:48 PM

Consult Review

Submission: NDA 212642
Sponsor: UCSF and UCLA

Product: **Ga 68 -PSMA-11**
Consult Request: **Labeling, Dosimetry**

Reviewer: Kish Chakrabarti, PhD, FAAPM, DIRM
Clinical Team Lead: Anthony Fotenos, MD, Ph.D, DIRM
Through Division Deputy Director: Alex Gorovets, MD, DIRM

Executive Summary:

[Redacted content] (b) (4)

The sponsor should be advised [Redacted content] (b) (4)

Review:

Dosimetry

The sponsor states that at the time of its analysis (August 2018), there were 3 publications that had provided dosimetry information for 68Ga-PSMA-11. Those were (Afshar-Oromieh et al., 2016, Green et al., 2017, and Pfob et al., 2016). The sponsor adapted Green and Afshar-Oromieh work, combined the dose measured in these 2 papers to determine a combined estimate of patient dose. They recalculated the organ doses for the individual patients from the Green cohort and **used OLINDA method** and software. **MIRD dose schema** was used, with activity from 6 target regions (kidneys, liver, spleen, bladder, pancreas, and the whole body). This dose includes the dose from the **511 keV annihilation** radiation as well as the emitted positron.

Kidneys are the critical organ. The sponsor estimated value (from the dose table) absorbed in kidneys was .3714 mGy/MBq

Green et al. estimated an absorbed kidney dose of 0.413 mGy/MBq .

Afshar-Oromieh, et al. similarly concluded that the kidneys are the critical organ, arriving at an estimated renal dose of 0.26 mGy/MBq.

Pfob, et al. report a renal adsorbed dose of only 0.121 mGy/MBq.

The following table provides more specific information from the published papers:

Publications	Study Objects	Patients	Delivered	Critical Organ Dose	Diuretic used
Green 2017	To estimate the human radiation dosimetry for 68Ga-PSMA-11	9 patients	112.5 ± 3.3 MBq	Kidneys with mean absorbed dose 0.413 mGy/MBq	
Afsar-Oromieh 2016	To explore human dosimetry and data on optimal timing of PET imaging after injection	4 patients	152-198 MBq	ighest tracer uptake was observed in the kidneys,kidneys 0.262 ± 0.098 mGy/MBq	
Pfob 2016	To evaluate the whole-body distribution and radiation dosimetry	5 patients	139.8 ± 13.7 MBq (120-158 MBq)	kidneys (median absorbed dose 1.21E-01 mGv/MBq;	furosemide
Sandgren 2019	To determine the effective dose and organ doses from injection of 68Ga-PSMA-11 in a cohort of low risk PCa patients.	6 patients	133-178 MBq	The kidneys received approximately 40 mGy after an injection with 160MBq 68Ga-PSMA-11 .24mGy/MBq	

In its labeling the sponsor states that:

“Unless contraindicated, a diuretic expected to act within the (b) (4) uptake time period may be administered at time of radiotracer injection to (b) (4) potentially decrease artifact from radiotracer accumulation in the urinary bladder and ureters”

Comments:

Both the Green and Afshar-Omorieh papers **did not** use furosemide in their studies.

Pfob, et al. report a renal adsorbed dose of only 0.121 mGy/MBq, that study was **performed with concurrent administration of furosemide at an unspecified dose** to promote urine production and urinary clearance.

Afshar-Oromieh, et al. in their study of four subjects that included additional renal clearance data between 2 and 5 h. Differences in administered mass of PSMA-11 may also result in some changes in renal retention of the radiotracer, which, however, cannot be directly compared from the published data.

(b) (4)
It appears that bladder clearance resulting in low bladder activities can cause a lower estimate of kidney dose. This is observed by Afsher et al. who did not use any diuretic.

It is also observed (Nijara et al.) in FDG that the use of a relatively simple diuretic protocol can lower bladder FDG activity and potentially improve image quality by reducing bladder activity artifacts and avoid invasive bladder catheterization. It is more clearly evident that image quality of a PET image is improved with reduction of bladder artifact when furosemide is used in conjunction. Paucity of currently available published results indicate that dose reduction is not well established.

The sponsor should be advised (b) (4)

The sponsor states:

These radiation doses are for PSMA-11 Ga 68 alone. If CT or a transmission source are used for attenuation correction, the radiation dose will increase by an amount that varies by technique.

This is a necessary statement but not a sufficient one. In many dual PET/CT mode almost comparable doses are delivered by both modalities. It is therefore, important that we ask for the dose values from CT or ask the sponsor to specify the technique factors used.

References:

1. Mark A. Green a, Jacob A. Eitel a, James W. Fletcher, Carla J. Mathias, MarkA.Tann, Thomas Gardner, Michael O. Koch, Wendy Territo, Heather Polson, Gary D. Hutchins, Estimation of

radiation dosimetry for ^{68}Ga -HBED-CC (PSMA-11) in patients with suspected recurrence of prostate cancer, Nuclear Medicine and Biology 46 (2017) 32–35 [3]

2. Afshar-Oromieh A, Hetzheim H, Kübler W, Kratochwil C, Giesel FL, Hope TA, et al. Radiation dosimetry of ^{68}Ga -PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. Eur J Nucl Med Mol Imaging 2016;43:1611–20.
3. Pfob PH, Ziegler S, Graner FP, Köhner M, Schachoff S, Blechert B, et al. Biodistribution and radiation dosimetry of ^{68}Ga -PSMA HBED CC — a PSMA specific probe for PET im-aging of prostate cancer. Eur J Nucl Med Mol Imaging 2016;43:1962–7
4. Sundeep Nijjara, Judy Pattersona, Jaylene Ducharme, William D. Leslie, b and Sandor J. Demetera, The effect of furosemide dose timing on bladder activity in oncology imaging with ^{18}F -fluorodeoxyglucose PET/CT, Nuclear Medicine Communications 2010, Vol 31 No 2 160-172

Kish Chakrabarti

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/s/

KISHALAYA CHAKRABARTI
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ANTHONY F FOTENOS
05/18/2020 02:53:34 PM



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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DPMH PLLR Labeling Review

Date: May 8, 2020 **Date Consulted:** March 31, 2020

From: Jeanine Best, MSN RN, PNP, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health,
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Medical Imaging and Radiation Medicine (DMIRM)

Drug: Gallium Ga 68 PSMA-11 Injection

NDA: 212642

Applicant: University of California, Los Angeles

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication:  (b) (4)

Materials Reviewed:

- Applicant's draft labeling, submitted September 6, 2019.

Consult Question: The clinical team would like input regarding the correct labeling language which should be utilized in subsection 8.1 and 8.2.

BACKGROUND

On September 6, 2019, the University of California, Los Angeles, submitted an original NDA (NDA 212642), for Gallium Ga 68 PSMA-11 Injection, a radioactive diagnostic agent indicated for (b) (4)

The Division of Medical Imaging and Radiation Medicine (DMIRM) consulted the Division of Pediatric and Maternal Health (DPMH) on March 31, 2020, to provide input on pregnancy and lactation labeling language for compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

There are no previous DPMH reviews for Gallium Ga 68 PSMA-11 Injection.

Gallium Ga 68 PSMA-11 Drug Characteristics¹

- Established Pharmaceutical Class: Radiodiagnostic agent.
- Mechanism of Action: Binds to the prostate-specific membrane antigen (PSMA) and to cells that express PSMA including malignant prostate cancer cells, which overexpress PSMA.
- Ga 68 is a β^+ emitting radionuclide that allows positron emission tomography (PET) imaging.
- Accumulates preferentially in the liver, kidneys, spleen, and salivary glands. Uptake is also seen in the adrenals and prostate.
- Fourteen percent of the injected dose is excreted in urine in the first two hours post-injection.
- Radiation dosimetry table does not contain dosimetry information for female reproductive organs.

DISCUSSION/CONCLUSIONS

Pregnancy and Lactation

Gallium Ga 68 PSMA-11 is indicated for positron emission tomography (PET) imaging in men with prostate cancer. Clinical trials are underway for use of Ga 68 PSMA in diagnosing metastasis in females with ovarian cancer (NCT03857097) and in diagnosing thyroid cancer in patients (NCT03463889).

Although, Ga 68 PSMA-11 is currently indicated only in men, there is potential for off-label use in females of reproductive potential; therefore, labeling should contain limited information regarding use in pregnancy and lactation, but not infer the product is indicated in this population. Pregnancy and lactation labeling should contain statements

¹ Refer to applicant submitted labeling, 9/6/2019

that Ga 68 PSMA is not approved in females. Subsection 8.1 Pregnancy should contain radiopharmaceutical class language that potential fetal harm Ga 68 PSMA-11 depends on the fetal stage of development and the magnitude of the radiation dose. The (b) (4) statement should be omitted from labeling.

(b) (4)

RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of Gallium Ga 68 PSMA-11 labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on May 5, 2020. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Ga 68 PSMA-11 Injection is not indicated for use in females. There are no available data with Ga 68 PSMA-11 Injection use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. All radiopharmaceuticals, including Ga 68 PSMA-11 Injection have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of radiation dose. Animal reproduction studies have not been conducted with Ga 68 PSMA-11 Injection.

8.2 Lactation

Risk Summary

Ga 68 PSMA-11 Injection is not indicated for use in females. There are no data on the presence of Ga 68 PSMA-11 Injection in human milk, the effect on the breastfed infant, or the effect on milk production.

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LYNNE P YAO
05/11/2020 11:29:07 AM

Clinical Inspection Summary

Date	April 15, 2020
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Diane Hanner, M.P.H., M.S.W., L.S.W., Regulatory Project Manager Shane Masters, M.D., Medical Officer August Hofling, M.D., Clinical Team Leader Division of Medical Imaging Products (DMIP)
Applications	NDA 212642 and NDA 212643
Applicants	NDA 212642: University of California, Los Angeles (UCLA) NDA 212643: University of California, San Francisco (UCSF)
Drug	PSMA-HBED-CC GA-68 (⁶⁸ Ga-PSMA-11)
NME / Original NDA	Yes
Review Status	Priority
Proposed Indication	(b) (4)
Consultation Date	September 25, 2019
CIS Goal Date	March 6, 2020 (original); April 20, 2020 (extended)
Action Goal Date	May 6, 2020
PDUFA Due Date	May 6, 2020

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Studies PSMA-PRERP and PSMA-BCR were audited at good clinical practice (**GCP**) inspections of two (all) clinical investigator (**CI**) sites. Each CI site participated in both studies, and each study was jointly sponsored by University of California, Los Angeles (**UCLA**, applicant for NDA 212642) and University of California, San Francisco (**UCSF**, applicant for NDA 212643). The two sponsors co-developed PSMA-HBED-CC GA-68 (^{68}Ga -PSMA-11) as a new molecular entity (**NME**) diagnostic imaging agent for use with positron emission tomography (**PET**) for the localization of prostate cancer (**PCa**) under two different clinical settings: in planning pre-radical prostatectomy (**PRERP**) as the initial definitive treatment for PCa (Study PSMA-PRERP), and subsequently to visualize PCa in case of biochemical recurrence (**BCR**) following PRERP (Study PSMA-BCR).

No significant GCP deficiencies were observed for either study. For both CI sites, study conduct appeared GCP-compliant, including institutional (sponsor) oversight. All audited data were adequately verifiable against source records and case report forms (**CRFs**). The data from the inspected CI sites appear reliable as reported in the NDA.

II. BACKGROUND

PCa is a leading cancer in men with the second highest mortality after lung cancer. Imaging is important to the diagnosis and monitoring of PCa, yet diagnostic accuracy has been relatively low for all currently available imaging methods (30-80%), including bone scan, pelvic computerized tomography (**CT**), magnetic resonance imaging (**MRI**), and PET. Imaging methods targeting the prostate-specific membrane antigen (**PSMA**) has been receiving increasing attention, particularly those using ^{68}Ga -labeled PSMA-11 and other PSMA ligands.

PET in combination with CT (**PET/CT**) using ^{68}Ga -labeled PSMA-11 has been touted recently to be superior to the currently available imaging methods in selected stages of PCa monitoring. The two sponsors jointly seek the approval of ^{68}Ga -PSMA-11 for use with PET in detecting and localizing PCa in support of shaping the initial and subsequent treatment strategy, to be manufactured at UCLA Biomedical Cyclotron Facility and at UCSF Radiopharmaceutical Facility for distribution to the clinics within the respective UCLA or UCSF Health Systems.

Study PSMA-PRERP: *^{68}Ga -PSMA-11 PET/CT in intermediate to high-risk prostatectomy patients*

This open-label single-arm study was conducted between December 2015 and October 2018 in 325 subjects (safety analysis set) with PCa at two CI sites (UCLA and UCSF). The major study objectives were to determine the subject-level variables (co-primary efficacy endpoints/analyses) of sensitivity (**Sn**), specificity (**Sp**), positive predictive value (**PPV**), and negative predictive value (**NPV**) of ^{68}Ga -PSMA-11 PET imaging in visualizing

regional nodal metastases relative to histopathology (at radical prostatectomy) as the standard of reference (**SoR**), and to evaluate the inter-reader concordance for the primary variables (secondary endpoints/analyses).

Adults with intermediate to high-risk PCa were enrolled if planning (or scheduled for) radical prostatectomy with lymph node dissection. A single 5 mCi (range 3-7 mCi) bolus intravenous (**IV**) injection of ^{68}Ga -PSMA-11 was followed in 75 minutes (range 50-100 minutes) by PET imaging. The imaging (efficacy) endpoint was the visualization of tumor by ^{68}Ga -PSMA-11 PET.

Study PSMA-BCR: *Ga-68 PSMA-11 positron emission tomography (PET) in patients with biochemical recurrence*

This open-label single-arm study was conducted between September 2016 and October 2017 in 635 subjects (safety analysis set) with PCa enrolled at the same two CI sites as in Study PSMA-PRERP. The primary study objective was to determine the PPV of ^{68}Ga -PSMA-11 PET in visualizing disease recurrence, by subject and by anatomic region.

Adults with PCa definitively treated by prostatectomy or radiation therapy were enrolled if disease recurrence was detected by rising prostate-specific antigen (**PSA**) and confirmed by biopsy (histopathology) of the recurrent lesion. A single injection of the study medication was followed by PET. The imaging efficacy endpoints were the visualization of the recurrent lesion, by ^{68}Ga -PSMA-11 PET (primary) and by conventional imaging (secondary). Data analyses were stratified by PSA.

III. INSPECTION RESULTS

1. Johannes Czernin, M.D.

University of California, Los Angeles
3201 South Maryland Parkway, Suite 318
Las Vegas, NV 89109

Inspection Dates: February 24 – March 5, 2020

Study PSMA-PRERP: 113 subjects screened and enrolled, 113 completed study

Study PSMA-BCR: 250 subjects screened and enrolled, 250 completed study

For each study, subject records were reviewed in detail for 25 subjects. Major NDA data listings were verified against on-site source records and CRFs: image read results, adverse events (**AEs**), and protocol deviations.

No significant deficiencies were observed for either study. Minor recordkeeping deficiency observations included inadequate summary documentation of otherwise adequate conduct and results recordation in determining subject eligibility. The overall study conduct appeared GCP-compliant, including institutional oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

2. Thomas A. Hope, M.D.

University of California, San Francisco
Box 0628, 505 Parnassus Avenue
San Francisco, CA 94143-0628

Inspection Dates: February 18 – 28, 2020

Study PSMA-PRERP: 211 subjects screened and enrolled, 210 completed study

Study PSMA-BCR: 385 subjects screened and enrolled, 384 completed study

For each study, subject records were reviewed in detail for 25 subjects. Major NDA data listings were verified against on-site source records and CRFs: image read results, AEs, and protocol deviations.

No significant deficiencies were observed for either study. The overall study conduct appeared GCP-compliant, including institutional oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Central Document Room / NDA 212642, NDA 212643

DMIP / Clinical Team Leader / August Hofling

DMIP / Medical Officer / Shane Masters

DMIP / Regulatory Project Manager / Diane Hanner

OSI / Office Director / David Burrow

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OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew

OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein

OSI / DCCE / GCPAB / Medical Officer / John Lee

OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague

OSI / Database Project Manager / Dana Walters

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/s/

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04/15/2020 04:02:32 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 2, 2020
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 212642
Product Name, Dosage Form, and Strength:	PSMA-11 Ga 68 Injection, 18.5 MBq/mL – 185 MBq/mL (0.5 mCi/mL – 5 mCi/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	University of California, Los Angeles
FDA Received Date:	September 6, 2019 and December 3, 2019
OSE RCM #:	2019-1879
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

University of California, Los Angeles Biomedical submitted NDA 212642 PSMA-11 Ga 68 Injection on September 6, 2019. PSMA-11 Ga 68 is a radioactive diagnostic agent proposed for

(b) (4)

We evaluated the proposed PSMA-11 Ga 68 Prescribing Information (PI) and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI) and container label for PSMA-11 Ga 68 to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI and container label for PSMA-11 Ga 68 identified areas of vulnerability that may lead to medication errors. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed PSMA-11 Ga 68 prescribing information (PI) and container label identified areas of vulnerability that may lead to medication errors. We provide recommendations for the Division in Section 4.1 and recommendations for University of California, Los Angeles in Section 4.2 below. We ask that the Division convey Section 4.2 in its

entirety to University of California, Los Angeles so that the recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DMIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

- a. Revise first bullet to read "Use aseptic technique and radiation shielding to maintain sterility during all operations involved in the manipulation and administration of PSMA-11 Ga 68." to ensure proper technique is used for user safety.
- b. We recommend moving the second bullet regarding the recommended dose of PSMA-11 Ga 68 to be the first bullet. In addition, revise to read "The recommended adult dose is 111 MBq to (b)(4) MBq (3 mCi to 7 mCi) as an intravenous injection. (2.2)" for clarity.
- c. We advise adding the statement "See full prescribing information for additional preparation, administration, imaging, and radiation dosimetry information (2)" as the last bullet point in the Dosage and Administration section.
- d. To increase readability of important information consider including units of measurement after each numeric value (i.e. revise "111 to (b)(4) MBq to 111 MBq to (b)(4) MBq").

B. Prescribing Information

1. Section 2: Dosage and Administration Section

- a. The recommended dose in Section 2.2 is listed as mCi with the MBq in parenthesis while the dose in the Highlights section is listed as MBq with the mCi in parenthesis. We recommend consistency among the Prescribing Information for dosage information to prevent confusion and medication errors.
- b. Section 2.2 provides instructions for Recommended Dosage and Administration, and Section 2.4 provides information on Administration. We recommend moving Section 2.4 to be incorporated in Section 2.2 in order to improve readability as some of the information is repetitive. Section 2.2 should be revised to include the separate subheadings "Recommended Dose" and "Administration" to improve readability.
- c. Under "Administration" subheading the first bullet should include specific aseptic technique information, second bullet on calculating volume, third bullet on visual inspection, fourth bullet on assaying final dose prior to administration, fifth bullet on flushing line, and sixth bullet on disposal. This will follow flow of administration and will provide clarity.

2. Section 16: How Supplied/Storage and Handling
 - a. Revise first statement of Section 16.1 How Supplied to read “PSMA-11 Ga 68 Injection (NDC [REDACTED]^{(b) (4)}) is supplied as a clear, colorless injection in a capped glass vial containing between 18.5 MBq/mL to 185 MBq/mL (0.5 mCi/mL to 5 mCi/mL), of PSMA-11 Ga 68 at calibration time, in approximately 12 mL”.
 - b. Provide subheadings in Section 16.2 Storage and Handling to separate out the Storage information and the Handling information.

4.2 RECOMMENDATIONS FOR UNIVERSITY OF CALIFORNIA, LOS ANGELES

We recommend the following be implemented prior to approval of this NDA:

A. Container Label

1. As currently presented, the route of administration statement blends in with the rest of the text on the label. Revise statement to read “For Intravenous Use Only” and increase the prominence of the statement.
2. The presentation of the strength at calibration is not consistent with the Prescribing Information (PI) which presents the concentration in MBq and mCi. Revise the concentration to align with the PI and present the strength in terms of MBq with mCi equivalents in parentheses.
3. Add unit of measure after each numeric value to increase readability and to prevent confusion (i.e. revise 0.5-5 mCi to 0.5 mCi to 5 mCi).
4. We recommend moving the expiration date/time information above with the rest of the information that will be filled in by the user to prevent confusion. In addition, we recommend removing the [REDACTED]^{(b) (4)} and replacing with a blank line for end users to fill that in as end users may use different formats of the date. In addition, remove the other [REDACTED]^{(b) (4)} as well on the label and replace with blank lines.
5. We recommend removing [REDACTED]^{(b) (4)} as this information is not required here and may lead to confusion.
6. Usual dosage statement is missing from the label per 21 CFR 201.55. We recommend adding “Recommended Dosage: See Prescribing Information”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for PSMA-11 Ga 68 received on September 6, 2019 from University of California, Los Angeles.

Table 2. Relevant Product Information for PSMA-11 Ga 68	
Initial Approval Date	N/A
Active Ingredient	PSMA-11 Ga 68
Indication	(b) (4)
Route of Administration	Intravenous Injection
Dosage Form	Injection
Strength	18.5 MBq/mL – 185 MBq/mL (0.5 mCi/mL – 5 mCi/mL)
Dose and Frequency	111-(b) (4) MBq (3-7mCi) as a bolus intravenous injection
How Supplied	(b) (4)
Storage	Store upright in a lead shielded container at 25°C (77°C); excursions permitted to 15°C - 30°C (59°F - 86°F).
Container Closure	Store in original container in radiation shielding.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following PSMA-11 Ga 68 labels and labeling submitted by University of California, Los Angeles.

- Container label received on September 6, 2019
- Prescribing Information (Image not shown) received on December 3, 2019, available from <\\cdsesub1\evsprod\nda212642\0003\m1\us\draft-labeling-text.pdf>

G.2 Label and Labeling Images

- Container Label



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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03/02/2020 12:43:05 PM

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03/02/2020 01:00:18 PM

Division of Oncology 1 Consultation (Clinical)

NDA# 212642 and NDA 212643

Date: 01/15/2020

Requesting Individual: Diane Hanner (DMIP), Shane Masters

Primary Reviewer: Mitchell Anscher, MD; Medical Officer, DO1, OOD/OND/CDER/FDA

Secondary Reviewer: Daniel Suzman, MD; Team Leader, DO1, OOD/OND/CDER/FDA

Requested Action

Clinical question: Considering the observed diagnostic performance of ^{68}Ga -PSMA-11 PET for identifying lymph node metastasis in pre-prostatectomy patients, is there potential clinical utility for its use in the initial staging of intermediate- to high-risk primary prostate cancer?

Background: Prostate cancer is the most commonly diagnosed cancer in US males, with 191,930 new cases estimated in 2020 and 33,330 deaths. Approximately 78% of men are diagnosed with localized disease, whereas approximately 12% will present with regional spread to lymph nodes. In patients with at least a 10% risk of lymph node metastases by currently available nomograms, current guidelines recommend cross-sectional imaging of the pelvis $\pm$ abdomen using CT or MRI. These imaging modalities suffer from poor diagnostic sensitivity (~40-45%), as they generally rely on size criteria rather than alterations in the normal lymph node internal architecture to detect nodal metastases. Thus, pelvic lymph node dissection remains the gold standard for detecting spread to regional nodes.

Extended pelvic lymph node dissections are currently recommended if the nomogram-predicted risk of lymph node spread is $\geq 2\%$ in the US and $\geq 5\%$ in Europe. The addition of a pelvic lymph node dissection to radical prostatectomy increases the risk of complications for the patient, and in most cases, no lymph node metastases are found. In addition, not all regions at high risk of spread are included in the procedure, such as the pre-sacral and peri-rectal nodes. Thus, better non-invasive diagnostic tests are needed to assess patients with prostate cancer for spread to regional lymph nodes at the time of diagnosis.

This issue is important for several reasons. First, the finding of regional lymph node metastases automatically places a patient into the NCCN very high-risk category and is likely to impact treatment recommendations following surgery. Second, prostate cancer is a disease of older men, many of whom have underlying medical conditions that preclude pelvic lymph node dissection, yet treatment for their prostate cancer may still be necessary and optimal treatment recommendations depend on accurate staging information. Finally, many men who may be candidates for surgery choose alternatives to surgery as their primary treatment approach, such as radiation therapy, and an accurate assessment of the status of their pelvic lymph nodes will impact on non-surgical treatment recommendations, too.

Molecular imaging offers an opportunity for improvement in detection rates, in that these techniques do not rely solely on size criteria to diagnose the presence of lymph node metastases. However, as these approaches have utilized PET/CT, which suffers from limitations in spatial resolution, especially for metastases $< 5\text{mm}$ in size, they have not been incorporated into current guidelines for the work-up of newly diagnosed patients. Two PET tracers, C11-choline and F18-fluciclovine, have been approved for

imaging of patients with biochemical recurrence but neither has been approved for diagnosis prior to primary treatment. Furthermore, the extremely short half-life of C11 requires on-site generation of the tracer, making it impractical for most US centers. Thus, there remains a large unmet need for better non-invasive diagnostic testing for staging of prostate cancer patients prior to definitive therapy.

Reviewer comment: The sponsor presented efficacy results in 127 patients enrolled at the time of initial staging prior to prostatectomy (RP). An additional 198 patients were imaged but did not go on to prostatectomy. Of the 127 patients who went on to RP, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 0.47 (95% CI: 0.31-0.61), 0.92 (0.86-0.96), 0.64 (0.48-0.77) and 0.85 (0.81-0.88), respectively. The primary endpoint of sensitivity ≥ 0.65 was not met. Compared to a published meta-analysis, the present study fell outside of the 95% CI for sensitivity [0.74 (0.51-0.89)]. The reason for the inferior results of the present submission is not clear. In both the present analysis and the meta-analysis, imaging was confirmed by histologic evaluation. In subgroup analyses of the current submission, there was a marked improvement in sensitivity and PPV in patients with Gleason score 8-10 vs 6-7 (sensitivity: GS 8-10--0.55 [0.43-0.66]; GS 6-7—0.25 [0.16-0.37]; PPV: GS 8-10—0.75 [0.64-0.84]; GS 6-7—0.33 [0.22-0.46]). There were 8 false positives, 6 of whom were probably true positives when the medical histories were reviewed. However, even including these patients as true positives, the primary endpoint was not met. There were 265 protocol violations reported. Inter-reader agreement for nodal metastases was good, 0.77 (0.67-0.87).

All patients in the study were to have intermediate-high risk adenocarcinoma of the prostate, as determined by PSA >10, T stage T2b or higher, Gleason score >6 or other factors, which in this case would be the UCSF CAPRA score. No patient was permitted to have had ADT or prior focal therapy, chemotherapy or radiotherapy. The PET images were read blindly by 6 randomly assigned nuclear medicine or radiology physicians and independently interpreted. Three independent reads per patient were obtained. Prior to beginning the readings, all readers underwent standardized training. Four anatomic regions were examined: prostate, pelvic nodes, extra-pelvic nodes and bone. Reader disagreement was resolved by majority vote. The statistical analysis plan called for an enrollment of 271 patients, assuming a 30% rate of nodal metastases in intermediate-high risk patients at RP. It was assumed 203/271 would undergo RP, yielding 61 patients with nodal metastases. A detection rate of 45% with conventional imaging for nodal metastases and a 65% detection rate on a per patient basis for PSMA PET were assumed for the purposes of study design, based on review of the literature.

Although the primary endpoint was not met and sensitivity results were inferior to other similar studies examining the potential role of Ga-68 PSMA PET/CT in prostate cancer before primary therapy, the results in the present submission were comparable to those of other cross-sectional imaging modalities (CT and MRI). In addition, for high risk patients for whom nuclear medicine bone scan is also recommended in addition to CT or MRI as part of routine staging, Ga-68 PET/CT may offer the advantage of complete radiographic staging with a single test.

Indications for treating the pelvic lymph nodes are not as well-defined for patients treated with definitive radiation therapy as they are for patients treated surgically. Short of biopsy-proven lymph node involvement, there is disagreement amongst radiation oncologists regarding criteria for pelvic lymph node radiation, as results of clinical trials addressing this issue have been conflicting. Furthermore, there is an increased risk of long-term toxicity with expansion of the radiation fields to include pelvic nodes, due to inclusion of larger volumes of bladder and bowel in the irradiated field. The finding of a negative Ga-68 PET/CT might support a decision to omit pelvic nodes from the radiation field. Conversely, a positive Ga-68 PET/CT would help support a decision to treat the lymph nodes. Whether a positive test would require confirmation by biopsy would be up to the treating physician and

would probably depend on the total constellation of risk factors for nodal spread for the individual patient.

For the purposes of implementing radiation therapy, the PET/CT images themselves might be sufficient for radiation planning, if the conditions required for simulation could be recreated on the PET/CT scanner, but in most cases, it would require a separate simulation with the option for fusion of the PET/CT images with the simulation CT.

The implications of false positive or false negative scans would be similar to that of false positive or false negatives with CT or MRI. Because of modest sensitivity of the test, the clinician will need to determine whether or not to treat lymph nodes based on the total constellation of risk factors for nodal spread and may employ one of the publicly available nomograms to assist in this determination. PET-negative nodes that are enlarged by CT or MRI criteria will likely require biopsy if possible. This approach is not different from that currently employed, and many clinicians are routinely obtaining a biopsy from areas of suspected nodal spread not only to confirm the presence of cancer, but also to try to identify potentially actionable mutations should primary treatment be unsuccessful.

Recommendation: It is the reviewer's opinion that there is a potential clinical utility for Ga-68 PSMA PET/CT in the pretreatment staging of men with prostate cancer. Based on the data presented, this potential utility would seem to be most apparent for men with high grade tumors (Gleason score 8-10), the presence of which would place men into the NCCN high risk category. The potential utility in men with intermediate risk tumors is less evident.

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