CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214032Orig1s000

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	214032
PDUFA Goal Date	December 23, 2021
OSE RCM #	2020-2418;2020-2021
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Associate Director for REMS	Laura Zendel, Pharm.D.
Design and Evaluation	
Review Completion Date	December 10, 2021
Subject	Review to determine if a REMS is necessary
Established Name	kit for the preparation of gallium (Ga)-68 gozetotide injection
Trade Name	Illuccix
Name of Applicant	Telix Pharmaceuticals US Inc.
Therapeutic Class	radiopharmaceutical
Formulation(s)	Injection: Each vial would contain up to 50 mCi (1,850 MBq) contains 7.5 mL of sterile solution of Ga 68 gozetotide at a strength of up to 6.7 mCi (247 MBq) per mL.
Dosing Regimen	The recommended amount of radioactivity to be administered for PET in adult is 3 mCi to 7 mCi (111 MBq to 259 MBq) administered as an intravenous bolus injection.

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Illuccix (kit for the preparation of gallium (Ga)-68 gozetotide injection; also knows as Ga-68 PSMA-11 injection) is necessary to ensure the benefits outweigh its risks. Telix Pharmaceuticals US, Inc. submitted a New Drug Application (NDA) 214032 for Ga-68 gozetotide injection with the proposed indication (b) (4) (b) (4) The serious risks associated with the use of Ga-68 gozetotide injection are risks for misdiagnosis and radiation exposure. The applicant did not submit a REMS or proposed risk management plan with this application but proposed describing these risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

The Division of Risk Management (DRM) and the Division of Imaging and Radiation Medicine (DIRM) have determined that if approved, a REMS is not necessary to ensure the benefits of Ga-68 gozetotide injection outweigh its risks. Ga-68 gozetotide injection appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available for approved Ga-68 PSMA-11 injection under NDA 212643 and as an acceptable scientific bridge between the kit for preparation of Ga-68 gozetotide injection and the approved Ga-68 PSMA-11 injection under NDA 212643 has been provided, the clinical reviewers stated that Ga-68 gozetotide injection shows clinically meaningful benefit, and recommend approval of Ga-68 gozetotide injection as a radioactive diagnostic agent indicated for PET of 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.

The most concerning adverse reactions observed with the use of Ga-68 gozetotide injection are risks for misdiagnosis and radiation exposure. If Ga-68 gozetotide injection is approved, labeling, including information in Warnings and Precautions and Patient Counseling Information, will be used to communicate the safety issues and management of toxicities associated with Ga-68 gozetotide injection.

1 Introduction

This review by DRM evaluates whether a REMS for the new molecular entity (NME) Illuccix (Ga-68 gozetotide injection) is necessary to ensure the benefits outweigh its risks. Telix Pharmaceuticals US, Inc. submitted a New Drug Application (NDA) 214032 for Ga-68 gozetotide injection with the proposed indication (b) (4) [1] The applicant did not submit a REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Ga-68 gozetotide injection (also knows as Ga-68 PSMA-11 injection[1]) is an NME submitted via the 505(b)(2) pathway application.[a] A 505(b)(2) NDA contains full safety and effectiveness reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant (FD&C Act, Section 505(b)(2)).[2] The efficacy and safety of Ga-68 gozetotide injection were evaluated under NDA 212643 (Ga-68 PSMA-11 injection[3]), which received FDA approval 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, as the primary support for the application.[4] It is a radioactive diagnostic agent that binds to cells that express prostate-specific membrane antigen (PSMA), including malignant prostate cancer cells, which usually overexpress PSMA. Ga-68 gozetotide is a β+ emitting radionuclide that allows PET.[1]

Ga-68 gozetotide injection is supplied as multiple-dose kit containing containing:

- Vial 1 (b) (4): 25 mcg gozetotide and 10 mcg D-mannose (stabilizer), as a lyophilized powder
- Vial 2 (b) (4): 150 mg anhydrous sodium acetate in HCl buffer, provider as either Vial 2A in Configuration A (for use with EZAG generator or cyclotron produced Ga 68 via GE FASTlab™) or Vial 2B in Configuration B (for use with IRE generator)
- Vial 3 (Empty (b) (4)) for the collection of gallium Ga 68 and radiolabeling reaction

After reconstitution and pH adjustment with acetate buffer and radiolabeling with Ga 68, Vial 3 is a multiple dose vial containing 7.5 mL of sterile solution of Ga 68 gozetotide at a strength of up to 6.7 mCi (247 MBq) per mL. Each vial would contain up to 50 mCi (1,850 MBq).

The recommended adult dose is 3 mCi to 7 mCi (111 MBq to 259 MBq) as a bolus intravenous injection.[b] Ga-68 gozetotide injection as a kit is not currently marketed in the United States, though injection (rather than kit) formulations have since been approved under NDA 212642 and NDA 212643.[3,4]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for Ga-68 gozetotide injection (NDA 214032) relevant to this review:

- 05/21/2019: Investigation New Drug (IND) 144421 submission for Ga-68 gozetotide .
- 09/23/2020: NDA 214032 submission for kit for the preparation of Ga-68 gozetotide injection with the proposed indication (b) (4) (b) (4)

[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.*

- 03/02/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Ga-68 gozetotide injection.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Prostate cancer is the most common cancer among men in the United States, representing the second most common cause of cancer-related death in men.[5] Malignant transformation of the prostate follows a multistep process, initiating as prostatic intraepithelial neoplasia (PIN) followed by localized prostate cancer, then advanced prostate adenocarcinoma with local invasion, culminating in metastatic prostate cancer.[6] Its greater prevalence in the west and migrant population data implicate lifestyle and environmental risk factors. Aside from age and race, the only established risk factor for prostate cancer is a family history of the disease. The risk for first-degree relatives of men with prostate cancer is about twice that for men in the general population. This familial risk is more than four times higher than that for the general population for men with first-degree relatives with prostate cancer diagnosed younger than 60 years.[7] The expected number of new cases of prostate cancer in the United States in 2021 is 248,530[c], with 34,130 expected deaths due to the disease[d].[8] Five-year survival for patients diagnosed with prostate cancer is approximately 97.5%.[9] Guidelines for advanced prostate cancer from the American Urological Association (AUA), American Society of Radiation Oncology (ASTRO), and Society of Urologic Oncology (SUO) define advanced prostate cancer by disease states including biochemical recurrence without metastatic disease after exhaustion of local treatment options, metastatic hormone-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, and metastatic castration-resistant prostate cancer.[10,11]

3.2 Description of Current Diagnostic Agents

Early detection and precise staging of prostate cancer are vital because the survival rate decreases dramatically when cancer has migrated beyond the prostate organ. Prostate-specific antigen (PSA)-based screening is one of the most common methods of prostate cancer diagnosis. Expression of PSA has also been reported in other tissues such as normal epithelium of the prostate, small intestine, kidney cells and salivary organs; however, the expression level in these parts is ~100–1000 fold lower than in prostate cancer.[12] After local therapy including surgery or radiation, the first sign of recurrence is typically a rising prostate specific antigen (PSA) in the absence of visible metastases. Currently, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) along with 99mTc-methylene diphosphonate bone scintigraphy remain the standard imaging approaches for post-treatment biochemical recurrence, although this is an evolving space. Clinicians may utilize novel PET-CT

[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.*

scans (eg, fluciclovine, choline, PSMA) in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging.[10] Advances in prostate cancer–specific PET (pcPET) have demonstrated new insights into patterns of disease recurrence. Emerging pcPET radiotracers including carbon 11 (C-11) choline, gallium 68 (Ga-68) PSMA, C-11 acetate, and 18F-fluorocyclobutane-1-carboxylic acid fluciclovine (FACBC) [fluciclovine F 18] provide opportunities to localize prostate cancer recurrence at an earlier state in the disease course when the PSA level is low, to inform medical decision-making, and to study PET-directed local therapy.[13]

Currently there are four pcPET radiotracers that have gained FDA approval in the United States for the indication of identifying recurrent prostate cancer. C-11 choline received FDA approval on September 12, 2012, for the indication of PET imaging of patients with suspected prostate cancer recurrence.[14] Fluciclovine F 18 received FDA approval on May 27, 2016, for prostate cancer patients with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment.[15] Ga-68 PSMA-11 received FDA approval 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.[3] Piflufolastat F 18 has recently approved by FDA on May 26, 2021 to detect recurrent or metastatic disease and stage patients with high risk prostate cancer.[16,17] The serious risks associated with C-11 choline and Ga-68 PSMA-11 are image misinterpretation and radiation exposure. The serious risks associated with fluciclovine F 18 and piflufolastat F 18 include image misinterpretation, hypersensitivity reaction and radiation exposure. None of these products have a boxed warning in their labels, nor was a REMS required for approval.[14,15,16,18] Ga-68 PSMA-11 injection and piflufolastat F 18 have recently been approved for use in the initial therapy and biochemical recurrence settings, but they are currently restricted in geographic availability.[4] Please refer to DIRM's Multi-disciplinary Review and Evaluation for a detailed analysis of current treatment options.[4]

Not all patients presenting to the treating oncologist fall into the relatively common clinical scenario of a rising PSA early after prostatectomy, however. Indeed, some patients present with rising PSA after definitive radiation therapy, whereas others present after they have received postprostatectomy radiation therapy, and others still after a late PSA rise years after initial surgery. Imaging with both a pcPET scan and a multiparametric MRI scan can provide complementary insight as to the location of recurrence.[13] Although the imaging of prostate cancer has made tremendous advances in recent years, due to tissue heterogeneity in prostate cancer, and the lack of specificity of conventional imaging techniques, difficulty remains in identifying small volumes of prostate cancer both in the gland and metastatic sites and no universally approved imaging methods exist for the early detection of prostate cancer.[12,19] There is a clear need for imaging strategies with new alternative modalities that target the extracellular domain of PSMA with high affinity and longer half-life, which allows for wider product distribution and accessibility to patients.

4 Benefit Assessment

The efficacy and safety of Ga-68 gozetotide injection were evaluated under NDA 212643 (Ga-68 PSMA-11 Injection[3]), which received FDA approval 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, as the primary support for the application (FD&C Act, Section 505(b)(2))[2].[4] The efficacy and safety of Ga-68 gozetotide injection were established in two prospective, open-label studies (PSMA-PreRP and PSMA-BCR) in men with prostate cancer.[1] At the time

of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for Ga-68 gozetotide injection.

4.1 PSMA-PRERP

In PSMA-PreRP, which is a two-center study, 325 patients were enrolled with biopsy-proven prostate cancer who were considered candidates for prostatectomy and pelvic lymph node dissection. All enrolled patients met at least one of the following criteria: serum PSA of at least 10 ng/mL, tumor stage cT2b or greater, or Gleason score greater than 6. Each patient received a single Ga 68 gozetotide PET/CT or PET/MR from mid-thigh to skull base.[1,3]

A total of 123 patients (38%) proceeded to standard-of-care prostatectomy and template pelvic lymph node dissection and had sufficient histopathology data for evaluation (evaluable patients). Three members of a pool of six central readers independently interpreted each PET scan for the presence of abnormal Ga 68 gozetotide uptake in pelvic lymph nodes located in the common iliac, external iliac, internal iliac, and obturator subregions bilaterally as well as in any other pelvic location. The readers were blinded to all clinical information except for the history of prostate cancer prior to definitive treatment. Extrapelvic sites and the prostate gland itself were not analyzed in this study. For each patient, Ga 68 gozetotide PET results and reference standard histopathology obtained from dissected pelvic lymph nodes were compared by region (left hemipelvis, right hemipelvis, and other). The median serum PSA was 11.8 ng/mL. The summed Gleason score was 7 for 44%, 8 for 20%, and 9 for 31% of the patients, with the remainder of the patients having Gleason scores of 6 or 10.[1,3]

Efficacy was established on the basis of the patient level sensitivity and specificity of Ga 68 gozetotide PET for the detection of regional nodal metastases against a histopathology results. An important secondary endpoint was positive and negative predictive value of Ga 68 gozetotide PET for the detection of regional nodal metastases compared to pathology at radical prostatectomy on a per patient basis.[20] Table 1 compares majority PET reads to pelvic lymph node histopathology results at the patient-level with region matching, such that at least one true positive region defines a true positive patient. As shown, approximately 24% of subjects studied were found to have pelvic nodal metastases based on histopathology (95% confidence interval: 17%, 32%).[e,1,4,3,20] Among the pool of six readers, sensitivity ranged from 36% to 60%, specificity from 83% to 96%, positive predictive value from 38% to 80%, and negative predictive value from 80% to 88%.[1,3]

Table 1: Patient-Level Performance of Ga 68 gozetotide PET for Detection of Pelvic Lymph Node Metastasis* in the PSMA-PreRP Study (n=123)[1,4,3,20,e]

		Histopathology		Predictive value** (95% CI)
		Positive	**Negative**	
PET scan	**Positive**	14	9	PPV 61% (41%, 81%)
	Negative	16	84	NPV 84% (79%, 91%)

[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*

Total	30	93	
Diagnostic performance (95% CI)	Sensitivity 47% (29%, 65%)	Specificity 90% (84%, 96%)	
*with region matching where at least one true positive region defines a true positive patient **PPV: positive predictive value, NPV: negative predictive value			

In an exploratory subgroup analysis based on summed Gleason score, there was a numerical trend toward more true positives in patients with Gleason score of 8 or higher compared to those with Gleason score of 7 or lower.[1,3]

4.2 PSMA-BCR

In PSMA-BCR, which is a two-center study, 635 patients were enrolled with biochemical evidence of recurrent prostate cancer after definitive therapy, defined by serum PSA of >0.2 ng/mL more than 6 weeks after prostatectomy or by an increase in serum PSA of at least 2 ng/mL above nadir after definitive radiotherapy. All patients received a single Ga 68 gozetotide PET/CT or PET/MR from mid-thigh to skull base. Three members of a pool of nine independent central readers evaluated each scan for the presence and regional location (20 subregions grouped into four regions) of abnormal Ga 68 gozetotide uptake suggestive of recurrent prostate cancer. The readers were blinded to all clinical information other than type of primary therapy and most recent serum PSA level. [1,3]

A total of 469 patients (74%) had at least one positive region detected by Ga 68 gozetotide PET majority read. The distribution of Ga 68 gozetotide PET positive regions was 34% bone, 25% prostate bed, 25% pelvic lymph node, and 17% extrapelvic soft tissue. Two hundred and ten patients had composite reference standard information collected in a PET positive region (evaluable patients), consisting of at least one of the following: histopathology, imaging (bone scintigraphy, CT, or MRI) acquired at baseline or within 12 months after Ga 68 gozetotide PET, or serial serum PSA. Composite reference standard information for Ga 68 gozetotide PET negative regions was not systematically collected in this study. The median serum PSA was 3.6 ng/mL. Prior treatment included radical prostatectomy in 64% and radiotherapy in 73%.[1,3]

Of the 210 evaluable patients, 192 patients (91%) were found to be true positive in one or more regions against the composite reference standard (95% confidence interval: 88%, 95%). Among the pool of nine readers used in the study, the proportion of patients who were true positive in one or more regions ranged from 82% to 97%.[e] The prostate bed had the lowest proportion of true positive results at the region-level (76% versus 96% for non-prostate regions).[1,3]

The likelihood of identifying a Ga 68 gozetotide PET positive lesion in this study generally increased with higher serum PSA level. Table 2 shows the patient-level Ga 68 gozetotide PET results stratified by serum PSA level. The mean time between PSA measurement and PET scan was 40 days with a range of 0 to 367 days. Percent PET positivity was calculated as the proportion of patients with a positive Ga 68 gozetotide PET out of all patients scanned. Percent PET positivity includes patients determined to be either true positive or false positive as well as those in whom such determination was not made due to the absence of composite reference standard data.

Table 2: Patient-Level Ga 68 gozetotide PET Results and Percent PET Positivity Stratified by Serum PSA Level in the PSMA-BCR Study (n=628)* [1,4,3,20,e]

PSA (ng/mL)	PET positive patients				PET negative patients	Percent PET positivity*** (95% CI)
	Total	TP**	FP**	Without reference standard		
		With reference standard				
<0.5	48	11	1	36	87	36% (27%, 44%)
		12				
≥0.5 and <1	44	15	3	26	35	56% (45%, 67%)
		18				
≥1 and <2	71	29	1	41	15	83% (75%, 91%)
		30				
≥2	299	137	13	149	29	91% (88%, 94%)
		150				
Total	462	192	18	252	166	74% (70%, 77%)
		210				

*7 patients were excluded from this table due to protocol deviations
**TP: true positive, FP: false positive
***Percent PET positivity = PET positive patients/total patients scanned

The clinical reviewer stated that an acceptable scientific bridge between the kit for preparation of Ga-68 gozetotide injection and the approved Ga-68 gozetotide injection under NDA 212643 has been provided. Please refer to DIRM's Multi-disciplinary Review and Evaluation for a detailed clinical review of efficacy.[4]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for Ga-68 gozetotide injection. The safety of Ga-68 gozetotide injection was evaluated in three studies, BCR-RET-01, PSMA-617-01 (NCT03511664), and ANMI-PG01-C301. In addition, the Applicant is relying on FDAs findings of safety for Ga-68 gozetotide injection under NDA 212643 (FD&C Act, Section 505(b)(2))[2]. Since ANMI-PG01-C301 was based on retrospective chart review without predefined safety data collection, and because no treatment emergent adverse events were reported in the study, it will not be discussed further.[4]

The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.[1]

Deaths

Two patient deaths were reported in PSMA-617-01. The first patient was a 71 year old man who had metastatic castrate resistant prostate cancer, dorsal pain, and asthenia. 46 days after administration of Ga-68 gozetotide injection he presented with sudden onset of central nervous system "aggravation." Head imaging showed brain hematomas, thought to be due to bleeding meningeal bone metastases. On day 47, the patient died. The investigator and Sponsor both assessed the events of anemia and brain hematomas as unrelated to Ga-68 gozetotide injection. The second patient was a 69 year old man with a history of metastatic castrate resistant prostate cancer, right lower extremity edema, abdominal

distention, and perennial rhinitis. 10 days after administration of Ga-68 gozetotide injection he was admitted to the hospital for pneumonia and treated with antibiotics. During this admission, he was also diagnosed with dermatomyositis. 22 days after administration of Ga-68 gozetotide injection he was admitted to the hospital due to dermatomyositis and on day 51 the patient died. The investigator assigned the cause of death as dermatomyositis. The investigator and Sponsor assessed the events of pneumonia and dermatomyositis as unrelated to Ga-68 gozetotide injection. Because the presence of metastatic prostate cancer can predispose to dermatomyositis and may also increase risk of infection through immunosuppression, this assessment is reasonable. The clinical reviewer assesssed that these deaths are unrleated to Ga-68 gozetotide injection.[4]

Serious Adverse Events (SAE)

A total of 21 treatment emergent SAEs were reported in PSMA-617-01, distributed among 11 patients. Four of these events in 2 patients are discussed in the prior section as they resulted in patient death. The clinical reviewer noted that most of the reported SAEs are either relatively common in older adults (i.e. gastritis, chest pain) or associated with metastatic prostate cancer and its treatment (i.e. anemia, bone pain, constipation).[4] No serious adverse reactions were attributed to Ga-68 PSMA-11 Injection under NDA 212643. No study dropouts or discontinuations due to adverse effects were reported in BCR-RET-01 or PSMA-617-01.[1]

If approved, labeling will include the following risks in the Warnings and Precautions section. Similar to other pcPE radiotracers such as Ga 68 gozetotide Injection under NDA 212643[3], labeling will include the risks for misdiagnosis and radiation exposure.

5.1 RISK MISDIAGNOSIS

Labeling will note that image misinterpretation errors can occur with Ga-68 gozetotide injection PET. The Warnings and Precautions section of the label communicates that a negative image does not rule out the presence of metastatic prostate cancer and a positive image does not confirm the presence of recurrent prostate cancer.[1]

5.2 RADIATION RISKS

Labeling will note that diagnostic radiopharmaceuticals, including Ga-68 gozetotide injection, expose patients to radiation and also note that the radiation exposure is associated with a dose-dependent increased risk of cancer. Labeling instructs to ensure safe handling and preparation procedures to protect patients and health care workers from unintentional radiation exposure. 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] At the Federal level, the Nuclear Regulatory Commission (NRC) has established rules to protect the general public, patients, and radiation workers from unnecessary exposure to radiation.[21,22]

6 Expected Postmarket Use

According to the current proposed indication, if approved, Ga-68 gozetotide injection will be administered by health care professionals with experience in managing radiolabeled products in

inpatient and outpatient licensed settings where these products are handled and administered routinely.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for Ga-68 gozetotide injection beyond routine pharmacovigilance and labeling. The applicant proposed describing these risks in the Prescribing Information that includes Warnings and Precautions, as well as information to be included in Patient Counseling Information.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for Ga-68 gozetotide injection, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Ga-68 gozetotide injection is a radioactive diagnostic agent, with the proposed indication for PET for the evaluation of prostate cancer. Based on the efficacy and safety information currently available for approved Ga-68 PSMA-11 injection under NDA 212643 and as an acceptable scientific bridge between the kit for preparation of Ga-68 gozetotide injection and the approved Ga-68 PSMA-11 injection under NDA 212643 has been provided, the clinical reviewers stated that Ga-68 gozetotide injection shows clinically meaningful benefit, and recommends approval of Ga-68 gozetotide injection as a radioactive diagnostic agent indicated for PET of 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.[1,4,f]

Prostate cancer is the most common cancer among men in the United States, representing the second most common cause of cancer-related death in men. Early detection and precise staging of prostate cancer are vital because the survival rate decreases dramatically when cancer has migrated beyond the prostate organ. Although the imaging of prostate cancer has made tremendous advances in recent years, due to tissue heterogeneity in prostate cancer and the lack of specificity of conventional imaging techniques, difficulty remains in identifying small volumes of prostate cancer both in the gland and metastatic sites and no universally approved imaging methods exist for the early detection of prostate cancer. There is a clear need for imaging strategies with new alternative modalities that targets the extracellular domain of PSMA with high affinity and longer half-life, which allows for wider product distribution and accessibility to patients. Ga-68 gozetotide injection appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.[1,4] Ga-68 gozetotide injection will be administered by health care professionals with experience in managing radiolabeled products in a licensed settings where these products are handled and administered routinely.

[f] Labeling negotiations were ongoing at the time of completion of this review. Indication statement is likely to be updated and significant changes to the proposed label likely to be made by FDA prior to negotiations.

DRM and DIRM have determined that if approved, a REMS is not necessary to ensure the benefits of Ga-68 gozetotide injection outweigh its risks. The most concerning adverse reactions observed with the use of Ga-68 gozetotide injection are risks for misdiagnosis and radiation exposure which are the same as the currently approved product which is approved without a REMS. At the time this review was completed, none of these risks will receive a boxed warning in the label, however labeling negotiations were still ongoing with the Applicant. If Ga-68 gozetotide injection is approved, similar to other pcPE radiotracers such as Ga-68 PSMA-11 Injection under NDA 212643[3], Warnings and Precautions in the labeling, will be used to communicate the safety issues and management of toxicities associated with Ga-68 gozetotide injection, as well as information to be included in Patient Counseling Information.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of Ga-68 gozetotide injection. The management of the risks associated with Ga-68 gozetotide injection treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

10 References

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