October 8, 2013

Materials Licensing Branch
U.S. NRC Region III
2443 Warrenville Rd.
Suite 210
Lisle, IL 60532-4352

Re: U.S. NRC Radioactive Materials License number 24-32517-01

Dear NRC Representative:

We would like to amend the above license to include the following items:

1. To add **Xofigo (Ra-223)** as a licensed byproduct (section 6). The requested maximum possession amount we would like to add is 1 Ci. We would like all our Authorized Users on the license who are currently licensed for byproducts under 10 CFR 35.300 to have authorized use capabilities for Ra-223. I have attached a template document with this letter which describes the Xofigo agent, dosage administration, and radiation safety measures.

Please feel free to contact me if you have further inquiry.

Thank you for you assistance in this matter.

Sincerely,

Stephen Howard, M.S.
Medical Physicist, RSO
Kansas City Cancer Centers
University of Kansas Cancer Center
Kansas City, MO 64131
Tel: 816-823-6659
Cell: 913-967-9056
Email: showard2@kumc.edu

University of Kansas Cancer Center

State of _____
Department of Radiologic Health
Attention: Radioactive Materials Licensing Section

Re: Request to Amend Radioactive Materials License # 24-32517-01

Steve Howard, RSO hereby requests that our Radioactive Materials License be amended to include:

1. Xofigo® (radium Ra 223 dichloride) injection with a maximum authorized possession limit of [1000000 µCi], and
2. See license, MD, to be listed as an Authorized User for Xofigo

Relevant program details are discussed below.

DESCRIPTION OF THE RADIOACTIVE THERAPEUTIC AGENT

Manufactured for: Bayer HealthCare Pharmaceuticals Incorporated (Made in Norway)

Distributed by: Cardinal Health central radiopharmacy

Indication: Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Activity: Xofigo is a ready-to-use radium 223 dichloride solution for direct intravenous injection (no mixing or dilution is involved). Sites will receive a unit dosage 10 mL syringe prepared by Cardinal Health central radiopharmacy. The ready-to-use injectable solution is neither mixed nor diluted onsite.

Physical Properties of Radium 223 and Xofigo: Radium 223 has a half-life of 11.4 days. The specific activity of radium 223 is 1.9 MBq (51.4 µCi)/ng.

The six-stage-decay of radium 223 to stable lead-207 occurs via short-lived daughters, and is accompanied predominantly by alpha emissions. There are also beta and gamma emissions with different energies and emission probabilities. The fraction of energy emitted from radium 223 and its daughters as alpha particles is 95.3% (energy range of 5 - 7.5 MeV). The fraction emitted as beta particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV), and the fraction emitted as gamma radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

The gamma radiation emission allows detection using standard nuclear medicine gamma detection survey instrumentation. Xofigo is not metabolized; fecal excretion is the major route of elimination from the body. (May need additional language from storage and handling guide)

PROPOSED AUTHORIZED USER(S)

See license, MD, is an American Board of Radiology (ABR)-certified Nuclear Medicine Physician or Radiation Oncologist currently authorized on our Radioactive Materials License 24-32517-01.

A copy of Dr. _____'s ABR certification is attached. As the Authorized User, Dr._____ will have responsibility and authority for radiation safety practices for the procedure.

RADIATION SAFETY, CONTAMINATION, AND CONTROL MEASURES

Standard radiation safety practices and hygiene measures will be used.

As stated, the Authorized User will have responsibility and authority for radiation safety practices for the procedure.

PACKAGE ORDERING AND RECEIPT

The radioactive therapeutic agent will be ordered as a unit dosage in accordance with written directive by the Authorized User.

The Type A-certified package will be delivered directly to and stored at the treating facility.

Appropriate documentation will be maintained per institutional policies

DOSE ADMINISTRATION

The therapy will be administered in a room posted as a restricted and controlled area as specified by state or federal regulations.

As stated, the gamma radiation associated with the decay of Ra 223 and its daughters allows for the radioactivity measurement of Xofigo exposure rate and the detection of contamination with standard survey instruments.

Radiation levels in unrestricted areas will be maintained less than the limits specified by state and federal requirements.

The external radiation exposure associated with handling of a patient dose is low; the treatment activity will be below 216 µCi (8,000 kBq).

Dosage level is 1.35 µCi (50 kBq)/kg body weight; which is approximately 95 µCi (3.5 MBq) for a 70 kg patient.

Treatment consists of 6 injections at 4-week intervals. Safety and efficacy beyond 6 injections with Xofigo have not been studied.

Each administration and treatment will be administered in accordance to the prescribing information.

PATIENT DISCHARGE

The patient exposure rate to others is <0.016 mR/hr at 1 meter for a 70 kg patient.

IMPORTANT SAFETY INFORMATION

- **Contraindications:** Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman

- **Bone Marrow Suppression:** In the randomized trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was similar for patients treated with Xofigo and placebo. Myelosuppression –notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia– has been reported in patients treated with Xofigo.

  Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure

- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 10^9/L, the platelet count ≥100 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 10^9/L and the platelet count ≥50 10^9/L. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care

- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued

- **Administration and Radiation Protection:** Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations

- **Adverse Reactions:** The most common adverse reactions (≥10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema. Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia

Please see accompanying full Prescribing Information.

WASTE MANAGEMENT

Any unused product or materials used will be treated as radioactive waste and disposed of in accordance with the Radioactive Materials License requirements and state and federal regulatory requirements.

Waste generated during patient treatment will be surveyed for radiation contamination with a portable Geiger Mueller (GM) low-range survey meter with scales in cpm or mR/hr and window thickness <7 mg/cm^2.

Contaminated waste will decay in storage until contamination levels are indistinguishable from natural background, a minimum of 10 half-lives.

We trust the following will meet with your approval. If you have any questions or require further details, please contact me at 913-967-9056.

Respectfully,

Radiation Safety Officer

Steve Howard, RSO

Enclosure: ABR Board Certification, Dr. See license

Please see accompanying full Prescribing Information.

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THE UNIVERSITY OF KANSAS CANCER CENTER

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