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David Rhoe
CRMI
Paseo de la Fuente
D-4 Calle Tivoli
San Juan, PR 00926-6459

December 30, 2013

USNRC Region I DNMS
2100 Renaissance Blvd
King of Prussia, PA 19406

RE: Amendment for CRMI license # 52-25430-03 03036911
Addition of Xofigo

Dear Sir or Madam:

An amendment (attached) was sent to the NRC in July 2013 for approval; a response has not been received.

1. Background. In the past the NRC required a statement in the license application or renewal process to read as follows:

   "This is to confirm that we will not be using alpha emitting unsealed byproducts materials."

   In accordance with the above, alpha emitters could not be used without an approved amendment. However, there is discordant

2. Requesting clarification: With the approval of Xofigo, are facilities required to apply for an amendment? According to telephone communications with NRC staff, the use of this pharmaceutical is approved under REG 35.300. However, this is 95.5% alpha emitter. Is the above license condition only for pure (100%) alpha emitters? Are all other alpha emitters that have beta and gamma emissions exempt? Please clarify in writing so I may forward this information to requesting facilities.

Sincerely,

David Rhoe
CEO

David Rhoe
CRMI
Paseo de la Fuente
D-4 Calle Tivoli
San Juan, PR 00926-6459

July 26, 2013

USNRC Region I DNMS
2100 Renaissance Blvd
King of Prussia, PA 19406

RE: Amendment for CRMI license # 52-25430-03
Addition of radium Ra 223 dichloride, which was approved by the FDA on May 15, 2013.

Dear Sir or Madam:

Please amend our NRC license to add the following isotope under 10 CFR Part 35, subpart E, which includes 35.300.

1. Xofigo® (radium Ra 223 dichloride) injection with a maximum authorized possession limit of [5 mCi].

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.

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. 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 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. 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 MEDICAL 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 ≥1.5 109/L, the platelet count ≥100 109/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 109/L and the platelet count ≥50

109/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.
600-60-0005-13 05/13 – attached.

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 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/cm2. Contaminated waste will decay in storage until contamination levels are indistinguishable from natural background

If your need any further information, please contact David Rhoe at 787-245-7248.

Sincerely,

David Rhoe
CEO

This is to acknowledge the receipt of your letter/application dated

12/30/13, and to inform you that the initial processing which includes an administrative review has been performed.

Notification (52-25430-03)

☒ There were no administrative omissions. Your application was assigned to a technical reviewer. Please note that the technical review may identify additional omissions or require additional information.

☐ Please provide to this office within 30 days of your receipt of this card

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A copy of your action has been forwarded to our License Fee & Accounts Receivable Branch, who will contact you separately if there is a fee issue involved.

Your action has been assigned **Mail Control Number** 582868.
When calling to inquire about this action, please refer to this control number.
You may call us on (610) 337-5398, or 337-5260.

NRC FORM 532 (RI)
(6-96)

Sincerely,
Licensing Assistance Team Leader