WHEELING™ HOSPITAL

The Schiffler Cancer Center
Gregory S. Merrick, M.D., Director
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Fax: (304) 243-5047 / (304) 243-7110

SchifflerCancerCenter@wheelinghospital.org

Br. 1

2 Apr 12

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(304) 243-3490

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Division of Nuclear Materials Licensing
U.S. NRC Region I
475 Allendale Road
King of Prussia, PA 19406-1415

RECEIVED
REGION 1
2012 APR -5 PM 12: 22

Re: License No. 47-05322-02 03012570

Dear US NRC:

Please amend our radioactive materials license to include the following unsealed byproduct material permitted under 10 CFR 35.300 (d):

Radium-223 chloride ($^{223}RaCl_2$) for intravenous injection.

The radiotherapeutic product is a clear and colorless solution supplied in glass vials, closed with rubber stoppers and aluminum crimp seals. The volume per vial is approximately 6 mL, corresponding to 6 MBq (0.16 mCi) and a radioactive concentration of 1000 kBq/mL (+/- 5 %) (0.03 mCi/mL) on calibration day. The radiopharmaceutical is manufactured for Bayer HealthCare by the Institute for Energy Technology (IFE), Isotope Laboratories, Kjeller, Norway.

The drug will be used in accordance with an Expanded Access Program, Investigational New Drug (IND) protocol accepted by FDA: clinicaltrials.gov identifier, NCT01516762.

A total possession limit of 37 MBq (1.0 mCi) is requested.

This request is detailed in the attached NRC Form 313 and supporting documents, including a printout of the web site, clinicaltrials.gov/ct2/show/NCT01516762, where Wheeling Hospital is listed on as one of 13 trial sites under Bayer sponsorship.

Also, please add radium-223 chloride ($^{223}RaCl_2$) to the items for which Dr. Gregory S. Merrick is an authorized user.

The decay of ^{223}Ra to stable ^{207}Pb has a half-life of 11.43 d and proceeds via short-lived radionuclides, primarily through alpha (α) particles (95.3% of total decay energy). However, 1.1% of the total energy is emitted as photons with a mean energy of 155 keV. These gamma (γ) rays will be used to measure the radiopharmaceutical to a prescribed dose of 50 kBq/kg of patient body weight in a dose calibrator and also to check for contamination with survey meters. Unused radiopharmaceutical and contaminated material such as syringes will be decayed in storage on site until the activity is indistinguishable from background radiation.

Training in the safe handling and administration of $^{223}RaCl_2$ will be coordinated with Bayer technical staff, and we will forward to the NRC copies of the completed training forms. Patients injected with $^{223}RaCl_2$ will have negligible

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NMSS/RGN1 MATERIALS-002

radiation dose rates external to their bodies, so they are immediately releasable. For example, the average patient weighing 70 kg receiving 3.5 MBq (95 μCi) would have an initial dose rate at 1 m < 0.35 μSv/h (0.035 mrem/h).

We are anxious to begin use of ^{223}Ra because it is the only radionuclide shown in clinical trials not only to relieve bone pain from metastatic prostate cancer but also to extend survival. The other radiopharmaceuticals we have tried do not change life expectancy. Metastron (^{89}Sr) provides only very modest pain palliation, and Quadramet (^{153}Sm) was only twice as effective as placebo (36% versus 18% for complete pain relief one month after injection.

Because radium and strontium are calcium analogs, the salts of those elements are avidly taken up in bone forming and bone destroying regions. Within bone, the very short penetration range of α-particles (< 0.1 mm) means that the metastatic bone disease will be targeted much more effectively than blood forming tissue. Clinical trial data indicate improvements in bone and disease markers such as prostate specific antigen (PSA) accompanied by negligible or minor myelosuppression. The quantitative measurements of disease remission and low toxicity are significantly superior to the older radiopharmaceuticals.

If you have any questions about this amendment request, please contact our authorized medical physicist, Dr. Wayne Butler at 304-243-3983 or e-mail him at wbutler@wheelinghospital.org.

Best regards,

Lisa N. Schatz

Lisa Schatz, Pharm.D.
Senior Clinical Director

NRC FORM 313 **U.S. NUCLEAR REGULATORY COMMISSION**
(1-2012)
10 CFR 30, 32, 33,
34, 35, 36, 39, and 40

APPLICATION FOR MATERIALS LICENSE

APPROVED BY OMB: NO. 3150-0120 **EXPIRES: (03/31/2012)**

Estimated burden per response to comply with this mandatory collection request: 4.3 hours. Submittal of the application is necessary to determine that the applicant is qualified and that adequate procedures exist to protect the public health and safety. Send comments regarding burden estimate to the Information Services Branch (T-5 F53), U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, or by internet e-mail to Infocollects.Resource@nrc.gov, and to the Desk Officer, Office of Information and Regulatory Affairs, NEOB-10202, (3150-0120), Office of Management and Budget, Washington, DC 20503. If a means used to impose an information collection does not display a currently valid OMB control number, the NRC may not conduct or sponsor, and a person is not required to respond to, the information collection.

INSTRUCTIONS: SEE THE APPROPRIATE LICENSE APPLICATION GUIDE FOR DETAILED INSTRUCTIONS FOR COMPLETING APPLICATION. SEND TWO COPIES OF THE ENTIRE COMPLETED APPLICATION TO THE NRC OFFICE SPECIFIED BELOW.

APPLICATION FOR DISTRIBUTION OF EXEMPT PRODUCTS FILE APPLICATIONS WITH:

OFFICE OF FEDERAL & STATE MATERIALS AND
ENVIRONMENTAL MANAGEMENT PROGRAMS
DIVISION OF MATERIALS SAFETY AND STATE AGREEMENTS
U.S. NUCLEAR REGULATORY COMMISSION
WASHINGTON, DC 20555-0001

ALL OTHER PERSONS FILE APPLICATIONS AS FOLLOWS:

IF YOU ARE LOCATED IN:

ALABAMA, CONNECTICUT, DELAWARE, DISTRICT OF COLUMBIA, FLORIDA, GEORGIA, KENTUCKY, MAINE, MARYLAND, MASSACHUSETTS, NEW HAMPSHIRE, NEW JERSEY, NEW YORK, NORTH CAROLINA, PENNSYLVANIA, PUERTO RICO, RHODE ISLAND, SOUTH CAROLINA, TENNESSEE, VERMONT, VIRGINIA, VIRGIN ISLANDS, OR WEST VIRGINIA,

SEND APPLICATIONS TO:

LICENSING ASSISTANCE TEAM
DIVISION OF NUCLEAR MATERIALS SAFETY
U.S. NUCLEAR REGULATORY COMMISSION, REGION I
475 ALLENDALE ROAD
KING OF PRUSSIA, PA 19406-1415

IF YOU ARE LOCATED IN:

ILLINOIS, INDIANA, IOWA, MICHIGAN, MINNESOTA, MISSOURI, OHIO, OR WISCONSIN, SEND APPLICATIONS TO:

MATERIALS LICENSING BRANCH
U.S. NUCLEAR REGULATORY COMMISSION, REGION III
2443 WARRENVILLE ROAD, SUITE 210
LISLE, IL 60532-4352

ALASKA, ARIZONA, ARKANSAS, CALIFORNIA, COLORADO, HAWAII, IDAHO, KANSAS, LOUISIANA, MISSISSIPPI, MONTANA, NEBRASKA, NEVADA, NEW MEXICO, NORTH DAKOTA, OKLAHOMA, OREGON, PACIFIC TRUST TERRITORIES, SOUTH DAKOTA, TEXAS, UTAH, WASHINGTON, OR WYOMING,

SEND APPLICATIONS TO:

NUCLEAR MATERIALS LICENSING BRANCH
U.S. NUCLEAR REGULATORY COMMISSION, REGION IV
1600 E. LAMAR BOULEVARD
ARLINGTON, TX 76011-4511

PERSONS LOCATED IN AGREEMENT STATES SEND APPLICATIONS TO THE U.S. NUCLEAR REGULATORY COMMISSION ONLY IF THEY WISH TO POSSESS AND USE LICENSED MATERIAL IN STATES SUBJECT TO U.S.NUCLEAR REGULATORY COMMISSION JURISDICTIONS.

1. THIS IS AN APPLICATION FOR *(Check appropriate item)*

- ☐ A. NEW LICENSE
- ☑ B. AMENDMENT TO LICENSE NUMBER 47-05322-02
- ☐ C. RENEWAL OF LICENSE NUMBER

2. NAME AND MAILING ADDRESS OF APPLICANT *(Include ZIP code)*

Lisa Schatz, Pharm.D., Senior Clinical Director
Wheeling Hospital
1 Medical Park
Wheeling, WV 26003

3. ADDRESS WHERE LICENSED MATERIAL WILL BE USED OR POSSESSED

Schiffler Cancer Center
Wheeling Hospital
1 Medical Park
Wheeling, WV 26003

4. NAME OF PERSON TO BE CONTACTED ABOUT THIS APPLICATION

Wayne M. Butler, Ph.D.

TELEPHONE NUMBER

(304) 243-3983

SUBMIT ITEMS 5 THROUGH 11 ON 8-1/2 X 11" PAPER. THE TYPE AND SCOPE OF INFORMAT ION TO BE PROVIDED IS DESCRIBED IN THE LICENSE APPLICATION GUIDE.

5. RADIOACTIVE MATERIAL.
a. Element and mass number; b. chemical and/or physical form; and c. maiximum amount which will be possessed at any one time.

6. PURPOSE(S) FOR WHICH LICENSED MATERIAL WILL BE USED.

7. INDIVIDUAL(S) RESPONSIBLE FOR RADIATION SAFETY PROGRAM AND THEIR TRAINING EXPERIENCE.

8. TRAINING FOR INDIVIDUALS WORKING IN OR FREQUENTING RESTRICTED AREAS.

9. FACILITIES AND EQUIPMENT.

10. RADIATION SAFETY PROGRAM.

11. WASTE MANAGEMENT.

12. LICENSE FEES *(See 10 CFR 170 and Section 170.31)*
FEE CATEGORY | AMOUNT ENCLOSED $

13. CERTIFICATION. *(Must be completed by applicant) THE APPLICANT UNDERSTANDS THAT ALL STATEMENTS AND REPRESENTATIONS MADE IN THIS APPLICATION ARE BINDING UPON THE APPLICANT.*

THE APPLICANT AND ANY OFFICIAL EXECUTING THIS CERTIFICATION ON BEHALF OF THE APPLICANT, NAMED IN ITEM 2, CERTIFY.THAT THIS APPLICATION IS PREPARED IN CONFORMITY WITH TITLE 10, CODE OF FEDERAL REGULATIONS, PARTS 30, 32, 33, 34, 35 , 36, 39, AND 40, AND THAT ALL INFORMATION CONTANED HEREIN IS TRUE AND CORRECT TO THE BEST OF THEIR KNOWLEDGE AND BELIEF.
WARNING: 18 U.S.C. SECTION 1001 ACT OF JUNE 25, 1948 62 STAT. 749 MAKES IT A C RIMINAL OFFENSE TO MAKE A WILLFULLY FALSE STATEMENT OR REPRESENTATION TO ANY DEPARTMENT OR AGENCY OF THE UNITED STATES AS TO ANY MATTER WITHIN ITS JURISDICTION.

CERTIFYING OFFICER -- TYPED/PRINTED NAME AND TITLE	SIGNATURE	DATE
Lisa Schatz, Pharm.D., Senior Clinical Director	Lisa N. Schatz, Pharm D	4/2/12

FOR NRC USE ONLY

TYPE OF FEE	FEE LOG	FEE CATEGORY	AMOUNT RECEIVED $	CHECK NUMBER	COMMENTS
APPROVED BY				DATE	

Re: Amendment to license number 47-05322-02

NRC Form 313, Item number:

5. RADIOACTIVE MATERIAL

   a. Element and mass number

      $^{223}Ra_{88}$ (radium-223)

   b. Chemical and/or physical form

      Radium-223 chloride ($^{223}RaCl_2$) as a clear, colorless solution for intravenous injection. The radiopharmaceutical solution will be delivered in a glass vial containing about 6 mL, corresponding to 6 MBq (0.16 mCi) and a radioactive concentration of 1000 kBq/mL (+/- 5 %) (0.03 mCi/mL) on calibration day. Delivery will be the day prior to calibration/injection, so the activity at delivery will be 4% to 5% hotter than the nominal 6 MBq.

   c. Maximum amount which will be possessed at any one time

      37 MBq (1.0 mCi) (Approximately six doses)

6. PURPOSE(S) FOR WHICH LICENSED MATERIAL WILL BE USED

   Castration-resistant (hormone-refractory) prostate cancer patients with bone metastases

   Treatment as per clinical trial NCT01516762 — one injection to be administered every 4 weeks at a dose of 50 kBq/kg body weight per injection and up to 6 injections per patient.

   Wheeling Hospital is listed on the web site, http://www.clinicaltrials.gov/ct2/show/NCT01516762, as one of 13 trial sites under Bayer sponsorship.

   The FDA has approved use of this radiopharmaceutical IND under its Expanded Access Program; therefore, we are requesting this NRC authorization under 10 CFR 35.300(d).

8. TRAINING FOR INDIVIDUALS WORKING IN OR FREQUENTING RESTRICTED AREAS

   Training in the safe handling and administration of $^{223}RaCl_2$ will be coordinated with Bayer technical staff, and we will forward to the NRC copies of the completed training forms.

   The primary users will be:

   Gregory S. Merrick, M.D. (Authorized User)

   Wayne M. Butler, Ph.D. (Authorized Medical Physicist)

Radium-223 Chloride (Alpharadin) in Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients With Bone Metastases

Expanded access is currently available for this treatment.

Verified March 2012 by Bayer

First Received on January 20, 2012. Last Updated on March 22, 2012 History of Changes

Sponsor:	Bayer
Information provided by:	Bayer
ClinicalTrials.gov Identifier:	NCT01516762

Purpose

This study is a prospective, interventional, open-label, multi-center early access program for the use of Ra-223 Cl in HRPC/CRPC patients diagnosed with symptomatic bone metastasis and to collect additional short and long term safety data on the product.

Condition	Intervention
Prostatic Neoplasms	Drug: Radium-223 chloride (BAY88-8223)

Study Type: Expanded Access What is Expanded Access?

Official Title: Radium-223 Chloride (Alpharadin) in Castration-Resistant (Hormone-Refractory) Prostate Cancer Patients With Bone Metastases

Resource links provided by NLM:

MedlinePlus related topics: Cancer Prostate Cancer

Drug Information available for: Chlorides

U.S. FDA Resources

Further study details as provided by Bayer:

Study Start Date: March 2012
Estimated Study Completion Date: June 2014
Estimated Primary Completion Date: June 2014 (Final data collection date for primary outcome measure)

Intervention Details:

Drug: Radium-223 chloride (BAY88-8223)
One injection to be administered every 4 weeks up to 6 injections. The dose per injection is 50 kBq/kg body weight.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Male

Criteria

Inclusion Criteria:

- Age ≥18 years
- Histologically or cytologically confirmed prostate cancer
- Patients diagnosed with symptomatic progressive bone predominant metastatic castrate-resistant / hormone-refractory prostate cancer (CRPC/HRPC) with at least 2 skeletal metastases on bone scan with no lung, liver, and/or brain metastasis (lymph node only metastasis is allowed)
    - Symptomatic is defined as either regular (not occasional) use of analgesic medication for cancer related bone pain (≥level 1;

WHO ladder for cancer pain), or treatment with EBRT for bone pain (the EBRT should be within the last 12 weeks before randomization)

- Progressive disease is defined either by:
  - The appearance of new bone lesions. If progression is based on new lesion(s) on bone scan only without an increase in prostate specific antigen (PSA), PSA values from 3 assessments within the last 6 months must be provided; OR
  - In the absence of new bone lesions by 2 consecutive increases in serum PSA over previous reference value, which should not be more than 6 months before screening, each measured at least 1 week apart with the last PSA ≥5 ng/mL
- No intention to use cytotoxic chemotherapy within the next 6 months
- Life expectancy ≥6 months
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 - 2
- Adequate hematological, liver, and renal function
  - Absolute neutrophil count (ANC) ≥1.5 x10^9/L
  - Platelet count ≥100 x10^9/L
  - Hemoglobin ≥10.0 g/dL (100 g/L; 6.2 mmol/L)
  - Total bilirubin level ≤1.5 x institutional upper limit of normal (ULN)
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN
  - Creatinine ≤1.5 x ULN
- Albumin > 25 g/L

Exclusion Criteria:

- Treatment with an investigational drug within previous 4 weeks, or planned during the treatment period or follow-up
- Eligible for first course of docetaxel, i.e., patients who are fit enough, willing, and who are located where treatment with docetaxel is available
- Treatment with cytotoxic chemotherapy within previous 4 weeks, or failure to recover from AEs due to cytotoxic chemotherapy administered more than 4 weeks previous (however, ongoing neuropathy is permitted)
- Received previous radiotherapy to > 25% of bone marrow, including hemibody radiation
- Received systemic therapy with radionuclides (e.g., strontium-89, samarium-153, rhenium-186, or rhenium-188, or radium-223 chloride) for the treatment of bony metastases
- Other malignancy treated within the last 3 years (except non melanoma skin cancer or low-grade superficial bladder cancer)
- Visceral metastases as assessed by abdominal or pelvic computed tomography (CT) (or other imaging modality)
- Presence of brain metastases
- Lymphadenopathy exceeding 6 cm in short-axis diameter
- Imminent or history of spinal cord compression based on clinical findings and/or magnetic resonance imaging (MRI)
- Any other serious illness or medical condition, such as but not limited to:
  - Any infection >/= National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 Grade 2
  - Cardiac failure New York Heart Association (NYHA) III or IV
  - Crohn's disease or ulcerative colitis
  - Bone marrow dysplasia
- Fecal incontinence

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01516762

Contacts

Contact: Bayer Clinical Trials Contact clinical-trials-contact@bayerhealthcare.com

Locations

United States, Arizona
Phoenix, Arizona, United States, 85013

United States, California
Laguna Hills, California, United States, 92653
Stanford, California, United States, 94305-5119

United States, Florida
Tampa, Florida, United States, 33612

United States, Louisiana
New Orleans, Louisiana, United States, 70112

United States, Massachusetts
Boston, Massachusetts, United States, 02215-5450

United States, Missouri

St. Louis, Missouri, United States, 63110

United States, Nevada
Las Vegas, Nevada, United States, 89169

United States, Pennsylvania
Pittsburgh, Pennsylvania, United States, 15213

United States, South Carolina
Myrtle Beach, South Carolina, United States, 29572

United States, Texas
Houston, Texas, United States, 77030-4009
Houston, Texas, United States, 77030-4298

United States, West Virginia
Wheeling, West Virginia, United States, 26003

Sponsors and Collaborators

Bayer

Investigators

Study Director: Bayer Study Director Bayer

More Information

Additional Information:

Click here and search for drug information provided by the FDA. EXIT

Click here and search for information on any recalls, market or product safety alerts by the FDA which might have occurred with this product. EXIT

No publications provided

Responsible Party:	Therapeutic Area Head, Bayer Healthcare AG
ClinicalTrials.gov Identifier:	NCT01516762 History of Changes
Other Study ID Numbers:	15995, 2011-004469-33
Study First Received:	January 20, 2012
Last Updated:	March 22, 2012
Health Authority:	United States: Food and Drug Administration

Keywords provided by Bayer:

- Radium 223
- Alpharadin
- Prostate Cancer
- Bone metastases
- Castrate resistant prostate cancer
- Hormone refractory prostate cancer

Additional relevant MeSH terms:

- Neoplasms
- Neoplasm Metastasis
- Prostatic Neoplasms
- Bone Neoplasms
- Bone Marrow Diseases
- Neoplastic Processes
- Pathologic Processes
- Genital Neoplasms, Male
- Urogenital Neoplasms
- Neoplasms by Site
- Genital Diseases, Male
- Prostatic Diseases
- Bone Diseases
- Musculoskeletal Diseases
- Hematologic Diseases
- Hormones
- Hormones, Hormone Substitutes, and Hormone Antagonists
- Physiological Effects of Drugs
- Pharmacologic Actions

ClinicalTrials.gov processed this record on March 29, 2012

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

4/2/12, and to inform you that the initial processing which includes an administrative review has been performed.

Amendment (47-05322-02)

☒ 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

_____.

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** 577287.
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