THERAPEUTIC RADIOPHARMACEUTICALS

Guideline Number: MMG161.B **Effective Date**: July 1, 2019

Instructions for Use

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Related Policies

None

COVERAGE RATIONALE

Azedra® (iobenguane I 131) injection for intravenous use is proven and medically necessary when ALL the following criteria are met:

- Member with positive iobenguane scan; **and**
- Member has unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Azedra® (iobenguane I 131) injection for intravenous use is unproven and not medically necessary for ALL other indications due to insufficient evidence of efficacy.

Lutathera® (lutetium Lu 177 dotatate) injection for intravenous use is proven and medically necessary for the treatment of somatostatin receptor-positive metastatic or unresectable locally advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults, who have progressed on a high dose somatostatin analog(e.g. long acting octreotide, lanreotide).

Lutathera® (lutetium Lu 177 dotatate) injection for intravenous use is unproven and not medically necessary for ALL other indications due to insufficient evidence of efficacy.

Radium-223 (Xofigio) is proven and medically necessary when ALL of the following criteria are met:

- Member has metastatic, castration-resistant prostate cancer (mCRCP); and
- Member has bone metastases documented on imaging; and
- Member is not/will not be receiving concurrent chemotherapy, biologic therapy, or immunotherapy (concurrent use of hormonal therapy is permitted); and
- Member has no current visceral metastatic disease.

Radium-223 (Xofigo®) is unproven and not medically necessary for ALL other indications due to insufficient evidence of efficacy.

DOCUMENTATION REQUIREMENTS

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

Required Clinical Information
Therapeutic Radiopharmaceuticals
Medical notes documenting **all** of the following: • Current prescription • Name and tax ID number of the servicing provider/facility to facilitate claim processing • Member diagnosis • Imaging reports demonstrating advancing disease • Previous treatments rendered and response • Requested dose, frequency, and interval

DEFINITIONS

Azedra® (iobenguane I 131): is a radioactive therapeutic agent indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

Carcinoid Syndrome: Carcinoid syndrome is a constellation of symptoms resulting from hormones secreted by carcinoid tumors. Active tumors secrete various hormones and vasoactive peptide substances such as adrenocorticotropic hormone (ACTH), serotonin, histamine, and tachykinins. (NCI 2018)

Lutathera® (lutetium Lu 177 dotatate): is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NET's), including foregut, midgut, and hindgut neuroendocrine tumors in adults. (NCI, 2018).

Neuroendocrine Tumor (NET): A tumor that forms from cells that release hormones into the blood in response to a signal from the nervous system. NETs may make higher-than-normal amounts of hormones, which can cause many different symptoms. These tumors may be benign (not cancerous) or malignant (cancerous) (NCI, 2018).

Pheochromocytoma: A rare tumor of the adrenal glands. These glands are located above the kidneys and make hormones including stress hormones called epinephrines and norepinephrines. Pheochromocytomas increase the production of these hormones, leading to hypertension (high blood pressure) and symptoms such as headaches, irritability, sweating, rapid heart rate, nausea, vomiting, weight loss, weakness, chest pain or anxiety. (NCI, 2018).

Radium-223 (Xofigo®): is an alpha-emitting radiotherapeutic drug. Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease. (NCI, 2018)

Somatostatin-Receptor Scintigraphy (SRS): A type of radionuclide scan used to find carcinoid and other types of tumors. Radioactive octreotide, a drug similar to somatostatin, is injected into a vein and travels through the bloodstream. The radioactive octreotide attaches to tumor cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide, and take pictures showing where the tumor cells are in the body; also called octreotide scan (NCI, 2018).

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

Coding Note: HCPCS codes A4641 or A9508 are intended to be reported for diagnostic use and are not appropriate for reporting therapeutic use of the radiopharmaceuticals addressed in this policy.

HCPCS Code	Description
A9513	Lutetium Lu 177, dotatate, therapeutic, 1 mCi
A9606	Radium RA-223 dichloride, therapeutic, per microcurie
A9699	Radiopharmaceutical, therapeutic, not otherwise classified

DESCRIPTION OF SERVICES

Therapeutic radiopharmaceutical agents are radioactive chemicals or drugs that have a specific affinity for a particular body tissue or organ. These agents are used alone and in conjunction with therapies to treat radiation-sensitive diseases.

Azedra® (iobenguane I 131)
Azedra® is a radioactive therapeutic indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. Pheochromocytomas are rare tumors that arise from cells of the sympathetic nervous system. Such tumors are usually found within one or both adrenal glands (85%), but may arise in other areas of sympathetic nerve cells, and are then referred to as paragangliomas. (Progenics, 2018).

Patients with PPGL may present with symptoms of excess catecholamine production, including hypertension, headache, perspiration, palpitations, tremor, and facial pallor. Episodes of hypertension can be variable in frequency, severity, and duration, and may be extremely difficult to manage medically. Hypertensive crisis can lead to cardiac arrhythmias, myocardial infarction, and death. Approximately 100 to 200 new cases of PPGL are diagnosed annually in the U.S. (Jimenez, 2018). PPGL is present in 0.1% to 1% of patients with hypertension; in children with hypertension, the prevalence of PPGL is approximately 1.7%. The incidence of pheochromocytoma is 2 to 8 per million persons per year, and it is present in approximately 5% of patients with incidentally discovered adrenal masses. The peak incidence occurs in the third to fifth decades of life (Lenders et al., 2014; National Cancer Institute, 2018).

Lutathera® (lutetium Lu 177 dotatate)
Lutathera® (lutetium Lu 177 dotatate) is a targeted form of radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults. Lutetium Lu 177 dotatate binds to a part of a cell called a somatostatin receptor, which may be present on certain tumors. After binding to the receptor, the drug enters the cell allowing radiation to cause damage to the tumor cells. (National Cancer Institute, 2018).

Neuroendocrine tumors (NETs) comprise a broad family of rare tumors which can arise from neuroendocrine cells in the diffuse neuroendocrine system anywhere in the body. Variations in clinical manifestations and biological characteristics of different NETs negatively impact timely diagnosis. Consequently, patients with NETs are often diagnosed only in their metastatic stage of malignancy. Late stage diagnosis further results in significant accrued morbidity burden and in a reduced survival rate. (Dasari, 2017; National Cancer Institute [NCI], 2018; National Comprehensive Cancer Network [NCCN], 2018).

Radium-223 (Xofigo®)
Xofigo (radium-223 dichloride) injection (Bayer HealthCare Pharmaceuticals Inc.), initially called Alpharadin, is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC) who have symptomatic bone metastases but no visceral metastases. It is a radioactive therapeutic agent that mimics calcium and selectively binds to areas of bone-repairing activity, forming complexes with bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases (Cheetham and Petrylak, 2012; Bayer HealthCare Pharmaceuticals Inc., 2013; Parker et al., 2013a).

Prostate cancer (PC) is the most common cancer in men and the second leading cause of cancer death in men. The annual incidence in the United States is approximately 242,000. Castration-resistant prostate cancer (CRPC) is defined by rising levels of prostate-specific antigen (PSA) in spite of androgen deprivation therapy and castrate levels of serum testosterone. Xofigo® (radium-223 dichloride) injection (Bayer HealthCare Pharmaceuticals Inc.) is intended for the treatment of patients with castrate-resistant prostate cancer (CRPC) with symptomatic bone metastases, and no visceral metastases. It is an alpha particle-emitting radioactive therapeutic agent that targets bone metastases by selectively binding to areas of bone-repairing activity, causing double-stranded breaks in DNA, but minimizing the effect on adjacent, healthy tissue (Hayes, Archived 2016).

CLINICAL EVIDENCE

Azedra® (iobenguane I 131)
The efficacy of Azedra was shown in a single-arm, open-label, clinical trial (NCT00874614) in 68 patients by determining the number of patients who experienced a 50 percent or greater reduction of all antihypertensive medications lasting for at least six months. This endpoint was supported by the secondary endpoint, overall tumor response measured by traditional imaging criteria. The study met the primary endpoint, with 17 (25 percent) of the 68 evaluable patients experiencing a 50 percent or greater reduction of all antihypertensive medication for at least six months. Overall tumor response was achieved in 15 (22 percent) of the patients studied.

Noto et al. 2018 conducted a phase I, open label, dose finding trial that evaluated Azedra in 21 adult patients with histologically confirmed evidence of recurrent or metastatic PPGL with at least one measurable lesion on computed tomography or magnetic resonance imaging that was also confirmed on a diagnostic iobenguane scan. Dose escalation was via a standard 3 + 3 design, starting at 222 megabecquerel per kilogram (MBq/kg) and escalating by 37 MBq/kg until the maximum tolerated dose was achieved. Overall, 14 patients (58%) completed the 12 month efficacy phase; none of these patients had a complete tumor response to treatment, and 4 (19%) had a partial response. Overall survival was 85.7% (18 of 21) at 1 year after treatment and 61.9% (13 of 21) at 2 years after treatment.

Lutathera® (lutetium Lu 177 dotatate)

Early case series and retrospective studies report that treatment of advanced GEP-NETs with lutetium Lu 177 dotatate was associated with tumor response, improved survival outcomes (such as, stable disease, tumor regression, or longer median time to progression), and quality of life (Delpassand, 2014; Ezziddin, 2014; Kwekkeboom, 2003; Kwekkeboom, 2005; Kwekkeboom, 2008; Sabet, 2014; Sabet, 2015; Teunissen, 2004).

In January 2018, the U.S. Food and Drug Administration approved Lutathera (lutetium Lu 177 dotatate) for the treatment of somatostatin receptor-positive GEP-NETs in adults, largely based on support from the NETTER-1 trial.

Strosberg et al. (2017) conducted an open-label, multicenter randomized, controlled trial evaluated the efficacy and safety of lutetium-177(^{177}Lu)–Dotatate in patients with advanced, progressive, somatostatin-receptor-positive midgut neuroendocrine tumors. 229 patients who had well-differentiated, metastatic midgut neuroendocrine tumors were randomized to receive either ^{177}Lu-Dotatate (116 patients) at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg) (^{177}Lu-Dotatate group) or octreotide LAR alone (113 patients) administered intramuscularly at a dose of 60 mg every 4 weeks (control group). The primary end point was progression-free survival. Secondary end points included the objective response rate, overall survival, safety, and the side-effect profile. The final analysis of overall survival will be conducted in the future as specified in the protocol. At the data-cutoff date for the primary analysis, the estimated rate of progression-free survival at month 20 was 65.2% (95% confidence interval [CI], 50.0 to 76.8) in the 1^{77}Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The response rate was 18% in the ^{177}Lu-Dotatate group versus 3% in the control group. The authors concluded that treatment with ^{177}Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Preliminary evidence of an overall survival benefit was seen in an interim analysis; confirmation will be required in the planned final analysis. Clinically significant myelosuppression occurred in less than 10% of patients in the ^{177}Lu-Dotatate group.

Brabander et al. (2017) reviewed a long-term safety and survival in an investigator-sponsored, open-label, single-arm, single-institution (Erasmus) retrospective study of over 1200 patients with somatostatin receptor positive neuroendocrine tumors who received ^{177}Lu-DOTATATE treatment. Primary tumor sites included bronchus, foregut, midgut, hindgut, pancreas and unknown. Patient populations were heterogeneous for baseline tumor status (progressive versus nonprogressive) and treatments received prior to ^{177}Lu-DOTATATE. Of these patients, the safety analysis included 610 patients, 360 (60%) of which had metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs), treated with a cumulative dose of at least 100 mCi (3.7 GBq) ^{177}Lu-DOTATATE. Long-term toxicity included acute leukemia in four patients (0.7%) and myelodysplastic syndrome in nine patients (1.5%). There was no therapy-related long-term renal or hepatic failure. Overall response rate, defined as complete or partial response, in patients with midgut and pancreatic NETs with progressive disease at baseline was 84% and 81%, respectively. Median overall survival for GEP-NETs was only reported for pancreas (71 months) and midgut (60 months), due to small numbers of other gastrointestinal primaries. A subset analysis of PFS in patients with midgut tumors and progressive disease at baseline was 24 months.

Professional Societies

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network's clinical practice guideline on "Neuroendocrine and Adrenal Tumors" (NCCN, 2018) recommends use lutetium Lu 177-dotatate for the treatment of somatostatin receptor-positive metastatic or unresectable locally advanced gastroenteropancreatic neuroendocrine tumors (NET), including foregut, midgut, and hindgut NET in adults who have progressed on octreotide or lanreotide..

Based on the clinical literature review from the studies noted below the evidence is sufficient to determine that treatment with lutetium Lu 177 dotatate results in meaningful improvement in net health outcomes for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut (gastroduodenal), midgut (distal small intestine and proximal colon), and hindgut (distal colorectal and pancreas) neuroendocrine tumors in adults.

Radium-223 (Xofigo®) for Treatment of Bone Metastases in Castration-Resistant Prostate Cancer (CRPC)

Nilsson, et al. (2012) examined the dose-response relationship and pain-relieving effect of Ra-223. A total of 100 patients with CRPC and painful bone metastases were randomized to Ra-223 vs. placebo. The primary end-point was pain index (visual analog scale [VAS] and analgesic use); pain index was also used to classify patients as "responders" or "non-responders". A significant dose response for pain index was noted at week 2, as well as week 8. The authors concluded that pain response was seen in up to 71 % of the patients with a dose response observed 2 weeks after administration; and the side effect profile of Ra-223 previously reported was confirmed, finding it to be well tolerated.

In a phase II, randomized, placebo-controlled study, Nilsson, et al. (2013) evaluated the safety and effectiveness of Ra-223 in patients with CRPC and painful bone metastases. The authors reported the 24-month OS and safety data from the period 12 to 24 months after the first injection of study medication. Patients with CRPC and bone pain were randomized 1:1 to receive 4 injections of Ra-223 (50 kBq/kg or placebo after external-beam radiotherapy; each injection was given every 4 weeks. End-points for this report were 24-month OS, long-term safety, and treatment-related adverse events (AEs) occurring in the 12- to 24-month period. After 24 months, 10 (30 %) patients were alive in the Ra-223 group compared with 4 patients (13 %) in the placebo group. Patients who received at least 1 dose of study medication had a median OS of 65 weeks in the Ra-223 group versus 46 weeks in the placebo group. The authors concluded that Ra-223 had a highly favorable safety profile, with no evidence of second malignancies at 24-month follow-up. The significant improvement in OS observed in patients receiving Ra-223 versus placebo suggested that treatment of bone disease with Ra-223 has survival benefits.

Parker et al. (2013a) performed a phase II, double-blind, multi-center clinical trial prospectively which evaluated the safety and effectiveness of 3 different doses of Ra-223 in patients with CRPC and bone metastases. A total of 122 patients were randomized to receive 3 injections of Ra-223 at 6-week intervals, at doses of 25 kBq/kg, 50 kBq/kg, or 80 kBq/kg. The study compared the proportion of patients in each dose group who had a confirmed decrease of greater than or equal to 50 % in baseline PSA levels. The study met its primary end-point with a statistically significant dose-response relationship being confirmed. The authors concluded that Ra-223 had a dose-dependent effect on serum markers of CRPC activity, suggesting that control of bone disease with Ra-223 may affect cancer-related outcomes.

Parker et al (2013b) also assessed the safety and effectiveness of Ra-223 in a phase III clinical trial. The investigators assessed the safety and effectiveness of Ra-223 as compared with placebo. These investigators randomly assigned 921 patients who had received, were not eligible to receive, or declined docetaxel, in a 2:1 ratio, to receive 6 injections of Ra-223 (at a dose of 50 kBq/kg intravenously) or matching placebo; 1 injection was administered every 4 weeks. Assessments of all main primary and secondary efficacy end-points also showed a benefit of Ra-233 as compared with placebo. Radium-223 was associated with low myelosuppression rates and fewer AEs. The authors concluded that in this study, which was terminated for efficacy at the pre-specified interim analysis, Ra-223 improved OS.

The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial was a phase 3, randomized, double-blind, placebo-controlled study which randomized 921 men with symptomatic bone-metastatic CRPC to six injections every weeks of either radium-223(50 kBq/kg) or placebo. Patients were symptomatic with two or more bone metastases, without visceral metastases and had received docetaxel or were ineligible for doxcetaxel treatment. Median overall survival in the radium-223 arm was 14.9 months compared to 11.2 months in the placebo arm. Median time-time-to-first skeletal related event was significantly improved in the treatment arm (13.6 months) compared to placebo (8.4 months). Time-to-alkaline-phosphatase-progression and time-to-PSA-progression was also improved in the treatment group. More adverse events were observed in the radium-223 group with discontinuation of treatment due to adverse events occurring in 13% of the men in the radium-223 and 20% of the men in the placebo arm. The significantly improved overall survival in the treatment group met the predetermined boundary for discontinuing the study early and the trial was terminated due to evidence of significant treatment benefit of radium-223. (Hoskin et al. 2014).

Parker et al. (2017) conducted a three-year safety evaluation of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Prostate Cancer Trial. Safety analyses from phase 3 randomized Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial included patients receiving ≥1 study-drug injection (600 radium-223 and 301 placebo). Patients (405 radium-223 and 167 placebo) entered long-term safety follow-up starting 12 wk after the last study-drug injection, to 3 yr from the first injection. Forty-eight of 405 (12%) radium-223 and 12/167 (7%) placebo patients completed follow-up, with evaluations every 2 mo for 6 mo, then every 4 mo until 3 yr. Final long-term safety ALSYMPCA analysis shows that radium-223 remained well tolerated, with low myelosuppression incidence and no new safety concerns.

Professional Societies

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network's clinical practice guideline on "Prostate cancer" (NCCN, 2017) recommends use of radium-223 as a first-line or second-line therapeutic option for CRPC in men with symptomatic bone metastases who do not have any visceral metastases. NCCN guidelines (2018) states that radium-223 is an

alpha-emitting radiopharmaceutical that has been shown to extend survival in men who have castrate-resistant prostate cancer with symptomatic bone metastases, but no visceral metastases.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

On July 30th, the S. Food and Drug Administration approved Azedra (iobenguane I 131) injection for intravenous use for the treatment of adults and adolescents age 12 and older with rare tumors of the adrenal gland (pheochromocytoma or paraganglioma) that cannot be surgically removed (unresectable), have spread beyond the original tumor site and require systemic anticancer therapy. The FDA granted this application Fast Track, Breakthrough Therapy and Priority Review designations. Azedra also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

In January 2018, the U.S. Food and Drug Administration approved Lutathera® (lutetium Lu 177 dotatate) for the treatment of somatostatin receptor-positive GEP-NETs in adults. This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. Lutathera® was approved under priority review and received Orphan Drug designation. GEP-NETs can be present in the pancreas and in different parts of the gastrointestinal tract such as the stomach, intestines, colon and rectum.

The FDA granted approval of radium Ra 223 dichloride (Xofigo®) injection based on a Phase III, double-blind, randomized, placebo-controlled clinical trial. The ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) trial included individuals with castration-resistant prostate cancer who had two or more bone metastases that were symptomatic.

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description

07/01/2019	• Updated policy template; added *Documentation Requirements* section
	• Revised coverage rationale:
	  ○ Simplified content
	  ○ Added language to indicate Azedra® (iobenguane I 131) injection for intravenous use is:
	  ▪ Proven and medically necessary when all the following criteria are met:
	  - Member with positive iobenguane scan; and
	  - Member has unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy
	  ▪ Unproven and not medically necessary for all other indications due to insufficient evidence of efficacy
	  ○ Replaced references to "individual" with "member"
	• Added definition of:
	  ○ Azedra® (iobenguane I 131)
	  ○ Pheochromocytoma
	• Updated list of applicable codes; added notation to clarify HCPCS codes A4641 and A9508 are intended to be reported for diagnostic use and are not appropriate for reporting therapeutic use of the radiopharmaceuticals addressed in this policy
	• Updated supporting information to reflect the most current description of services, clinical evidence, FDA information, and references
	• Archived previous policy version MMG161.A

INSTRUCTIONS FOR USE

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.