

CLINICAL APPROPRIATENESS GUIDELINES

RADIATION ONCOLOGY

Appropriate Use Criteria: Therapeutic Radiopharmaceuticals

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Proprietary

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Description and Application of the Guidelines

The AIM Clinical Appropriateness Guidelines (hereinafter “the AIM Clinical Appropriateness Guidelines” or the “Guidelines”) are designed to assist providers in making the most appropriate treatment decision for a specific clinical condition for an individual. As used by AIM, the Guidelines establish objective and evidence-based criteria for medical necessity determinations where possible. In the process, multiple functions are accomplished:

- To establish criteria for when services are medically necessary
- To assist the practitioner as an educational tool
- To encourage standardization of medical practice patterns
- To curtail the performance of inappropriate and/or duplicate services
- To advocate for patient safety concerns
- To enhance the quality of health care
- To promote the most efficient and cost-effective use of services

The AIM guideline development process complies with applicable accreditation standards, including the requirement that the Guidelines be developed with involvement from appropriate providers with current clinical expertise relevant to the Guidelines under review and be based on the most up-to-date clinical principles and best practices. Relevant citations are included in the References section attached to each Guideline. AIM reviews all of its Guidelines at least annually.

AIM makes its Guidelines publicly available on its website twenty-four hours a day, seven days a week. Copies of the AIM Clinical Appropriateness Guidelines are also available upon oral or written request. Although the Guidelines are publicly-available, AIM considers the Guidelines to be important, proprietary information of AIM, which cannot be sold, assigned, leased, licensed, reproduced or distributed without the written consent of AIM.

AIM applies objective and evidence-based criteria, and takes individual circumstances and the local delivery system into account when determining the medical appropriateness of health care services. The AIM Guidelines are just guidelines for the provision of specialty health services. These criteria are designed to guide both providers and reviewers to the most appropriate services based on a patient’s unique circumstances. In all cases, clinical judgment consistent with the standards of good medical practice should be used when applying the Guidelines. Guideline determinations are made based on the information provided at the time of the request. It is expected that medical necessity decisions may change as new information is provided or based on unique aspects of the patient’s condition. The treating clinician has final authority and responsibility for treatment decisions regarding the care of the patient and for justifying and demonstrating the existence of medical necessity for the requested service. The Guidelines are not a substitute for the experience and judgment of a physician or other health care professionals. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

The Guidelines do not address coverage, benefit or other plan specific issues. Applicable federal and state coverage mandates take precedence over these clinical guidelines. If requested by a health plan, AIM will review requests based on health plan medical policy/guidelines in lieu of the AIM Guidelines.

The Guidelines may also be used by the health plan or by AIM for purposes of provider education, or to review the medical necessity of services by any provider who has been notified of the need for medical necessity review, due to billing practices or claims that are not consistent with other providers in terms of frequency or some other manner.

General Clinical Guideline

Clinical Appropriateness Framework

Critical to any finding of clinical appropriateness under the guidelines for a specific diagnostic or therapeutic intervention are the following elements:

- Prior to any intervention, it is essential that the clinician confirm the diagnosis or establish its pretest likelihood based on a complete evaluation of the patient. This includes a history and physical examination and, where applicable, a review of relevant laboratory studies, diagnostic testing, and response to prior therapeutic intervention.
- The anticipated benefit of the recommended intervention should outweigh any potential harms that may result (net benefit).
- Current literature and/or standards of medical practice should support that the recommended intervention offers the greatest net benefit among competing alternatives.
- Based on the clinical evaluation, current literature, and standards of medical practice, there exists a reasonable likelihood that the intervention will change management and/or lead to an improved outcome for the patient.

If these elements are not established with respect to a given request, the determination of appropriateness will most likely require a peer-to-peer conversation to understand the individual and unique facts that would supersede the requirements set forth above. During the peer-to-peer conversation, factors such as patient acuity and setting of service may also be taken into account.

Simultaneous Ordering of Multiple Diagnostic or Therapeutic Interventions

Requests for multiple diagnostic or therapeutic interventions at the same time will often require a peer-to-peer conversation to understand the individual circumstances that support the medical necessity of performing all interventions simultaneously. This is based on the fact that appropriateness of additional intervention is often dependent on the outcome of the initial intervention.

Additionally, either of the following may apply:

- Current literature and/or standards of medical practice support that one of the requested diagnostic or therapeutic interventions is more appropriate in the clinical situation presented; or
- One of the diagnostic or therapeutic interventions requested is more likely to improve patient outcomes based on current literature and/or standards of medical practice.

Repeat Diagnostic Intervention

In general, repeated testing of the same anatomic location for the same indication should be limited to evaluation following an intervention, or when there is a change in clinical status such that additional testing is required to determine next steps in management. At times, it may be necessary to repeat a test using different techniques or protocols to clarify a finding or result of the original study.

Repeated testing for the same indication using the same or similar technology may be subject to additional review or require peer-to-peer conversation in the following scenarios:

- Repeated diagnostic testing at the same facility due to technical issues
- Repeated diagnostic testing requested at a different facility due to provider preference or quality concerns
- Repeated diagnostic testing of the same anatomic area based on persistent symptoms with no clinical change, treatment, or intervention since the previous study
- Repeated diagnostic testing of the same anatomic area by different providers for the same member over a short period of time

Repeat Therapeutic Intervention

In general, repeated therapeutic intervention in the same anatomic area is considered appropriate when the prior intervention proved effective or beneficial and the expected duration of relief has lapsed. A repeat intervention requested prior to the expected duration of relief is not appropriate unless it can be confirmed that the prior intervention was never administered.

Therapeutic Radiopharmaceuticals

General Information

Scope

These guidelines address the use of radiopharmaceutical therapy for oncologic conditions in both adult and pediatric populations. For interpretation of the Guidelines, and where not otherwise noted, “adult” refers to persons age 19 and older, and “pediatric” refers to persons age 18 and younger. Where separate indications exist, they are specified as adult or pediatric. Where not specified, indications and prerequisite information apply to persons of all ages.

See the Codes section for a list of modalities included in these guidelines.

Technology Considerations

Therapeutic radiopharmaceutical drugs (or radioactive drugs) contain a radioactive substance and are used to diagnose or treat disease, including cancer. Radioimmunotherapy specifically refers to systemic therapy that involves a targeting monoclonal antibody linked with a radiation-emitting radionuclide to treat certain types of cancer. These guidelines address the most commonly used radiopharmaceuticals.

Ibritumomab tiuxetan (Zevalin®) is a therapeutic radiopharmaceutical used for the treatment of certain types of B-cell non-Hodgkin lymphoma. It consists of an antibody which binds to the CD20 antigen found on the surface of B cells linked with the radioisotope yttrium-90. Ibritumomab tiuxetan was approved by the FDA in 2002 as a treatment for patients with relapsed or refractory CD20-positive non-Hodgkin lymphoma. The indications were expanded to include consolidative treatment of previously untreated follicular lymphoma after complete or partial response to first-line chemotherapy in 2009. Ibritumomab tiuxetan treatment is preceded by treatment with rituximab (Rituxan, an anti-CD20 monoclonal antibody) alone followed by rituximab in combination with ibritumomab tiuxetan.¹

Iobenguane I 131 (Azedra®) is a radioactive therapeutic agent approved by the FDA in 2018 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. I 131 decays with beta and gamma emissions with a physical half-life of 8.021 days. Iobenguane is taken up by the norepinephrine transporter in adrenergic nerve terminals and accumulates in adrenergically innervated tissues, such as the heart, lungs, adrenal medulla, salivary glands, liver, and spleen as well as tumors of neural crest origin. Pheochromocytoma and paraganglioma are tumors of neural crest origin that express high levels of the norepinephrine transporter on their cell surfaces. Following intravenous administration, iobenguane I 131 is taken up and accumulates within pheochromocytoma and paraganglioma cells, and radiation resulting from radioactive decay of I 131 causes cell death and tumor necrosis. Iobenguane I 131 is also called iodine I 131-metiodobenzylguanidine, 131I-MIBG, and Azedra; hereafter, it will be referred to as iobenguane I 131.²

Lutetium Lu 177-dotatate (Lutathera®) is a conjugate of radioactive lutetium and the somatostatin analog dotatate approved by the FDA in 2016. Lu 177-dotatate emits both beta and gamma rays and has a half-life of 6.64 days. Lutetium Lu 177-dotatate has been studied in the treatment of metastatic, well-differentiated neuroendocrine cancers that are somatostatin receptor positive. These tumors form from cells that release hormones and can occur in the stomach, small and large intestines, rectum, and pancreas. Lutetium Lu 177-dotatate is also being studied in the treatment of other types of cancer. Lutetium Lu 177-dotatate binds to receptors for a protein called somatostatin, which is found on some neuroendocrine tumor cells. Lutetium Lu 177-dotatate builds up in these cells and gives off radiation, which may help kill cancer cells. Lutetium Lu 177-dotatate is also called Lu 177-dotatate, 177Lu dotatate, and Lutathera; hereafter, it will be referred to as Lutetium Lu 177 dotatate.³

Radium Ra 223-dichloride (Xofigo®) is an alpha-emitting therapeutic radiopharmaceutical that was approved by the FDA in 2013 and has been shown to prolong survival in men with prostate cancer. In particular, it is used for the treatment of castration-resistant prostate cancer with symptomatic bone metastases. The drug causes double-stranded DNA breaks, but has a low risk of hematologic toxicity. It is administered monthly for 6 months,

and should be used as monotherapy (though it can be combined with hormonal agents or ablation). The use of radium 223 has been evaluated in combination with chemotherapy with early reports supporting efficacy. Radium 223 should be reserved for individuals with good functional status. Adequate bone marrow reserves should be confirmed prior to initial and subsequent administration and the drug should be discontinued if hematologic parameters do not recover within 6 to 8 weeks of an administered dose. It may cause bone marrow failure or prolonged pancytopenia, including risk of related death. Furthermore, in order to minimize the risk to the bone marrow, it is recommended that the patient meet the following requirements for safety purposes:

- No radioisotopes (such as Strontium or Samarium) over the previous 6 months (24 weeks)
- No chemotherapy or biologic therapy (hormonal therapy or ablation not included in biologic therapy) in the last 4 weeks.

Radium Ra 223-dichloride is also called Radium 223 and Xofigo; hereafter, it will be referred to as radium 223.⁴

Samarium Sm 153 lexidronam (Quadramet®) is a therapeutic radiopharmaceutical used to treat bone pain caused by primary bone cancer and other cancers that have spread to the bone. It consists of radioactive samarium and a tetrakisphosphonate chelator, ethylenediaminetetramethylenephosphonic acid, which emits both medium-energy beta particles and a gamma photon, and has a physical half-life of 46.3 hours (1.93 days). Samarium-153 has an average and maximum beta particle ranges in water of 0.5 mm and 3.0 mm, respectively. Samarium Sm 153-lexidronam pentasodium collects in bone and gives off radiation that may kill cancer cells. Samarium Sm 153-lexidronam is also called Sm 153, samarium-153 and Quadramet; hereafter, it will be referred to as Samarium 153.⁵

Sodium iodide I 131 is a radioisotope of iodine indicated for the treatment of hyperthyroidism and thyroid carcinomas that take up iodine. Oral sodium iodide I 131 is rapidly absorbed and distributed within the extracellular fluid of the body. Iodide is concentrated in the thyroid via the sodium/iodide symporter, and subsequently oxidized to iodine. I 131 decays by beta emission and associated gamma emission with a physical half-life of 8.04 days. Beta emission of sodium iodide I 131 destroys thyroid tissue. Sodium iodine I 131 is also called I 131; hereafter, it will be referred to as I 131.⁶

Strontium chloride Sr 89 is a therapeutic radiopharmaceutical used for the relief of bone pain in patients with painful skeletal metastases. Strontium 89 decays by beta emission with a physical half-life of 50.5 days. Following injection, strontium acts as a calcium analog and selectively localizes in mineralized bone. Uptake of strontium by bone occurs preferentially in sites of active osteogenesis; thus, primary bone tumors and areas of metastatic involvement can accumulate significantly greater concentrations of strontium than surrounding normal bone. Strontium chloride Sr 89 is also called Sr 89 and strontium 89; hereafter, it will be referred to as Strontium 89.⁷

Definitions

Statistical terminology

- **Confidence interval (CI)** – describes the amount of uncertainty associated with a sampling method. Confidence intervals are usually reported to help explain how reliable, or precise, a result is.⁸
- **Hazard ratio (HR)** – a measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.⁹
- **Odds ratio (OR)** – a measure of the odds of an event happening in one group compared to the odds of the same event happening in another group. In cancer research, odds ratios are most often used in case-control (backward looking) studies to find out if being exposed to a certain substance or other factor increases the risk of cancer. For example, researchers may study a group of individuals with cancer (cases) and another group without cancer (controls) to see how many people in each group were exposed to a certain substance or factor. They calculate the odds of exposure in both groups and then compare the odds. An odds ratio of one means that both groups had the same odds of exposure

and, therefore, the exposure probably does not increase the risk of cancer. An odds ratio of greater than one means that the exposure may increase the risk of cancer, and an odds ratio of less than one means that the exposure may reduce the risk of cancer. Also called relative odds.⁹

- **Overall survival (OS)** – length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the overall survival is one way to see how well a new treatment works.⁹
- **Overall survival rate** – percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease, such as cancer. The overall survival rate is often stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive five years after their diagnosis or the start of treatment. Also called survival rate.⁹
- **Progression-free survival (PFS)** – length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works.⁹
- **Relative risk (RR)** – a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group. In cancer research, relative risk is used in prospective (forward looking) studies, such as cohort studies and clinical trials. A relative risk of one means there is no difference between two groups in terms of their risk of cancer, based on whether or not they were exposed to a certain substance or factor, or how they responded to two treatments being compared. A relative risk of greater than one or of less than one usually means that being exposed to a certain substance or factor either increases (relative risk greater than one) or decreases (relative risk less than one) the risk of cancer, or that the treatments being compared do not have the same effects. Also called risk ratio.⁹
- **Response rate** – the percentage of patients whose cancer shrinks or disappears after treatment.⁹

Clinical Indications

Bone Metastases

A single dose of strontium 89 or samarium 153 (Quadramet®) is considered **medically necessary** for symptomatic bone metastases when **BOTH** of the following conditions are met:

- Confirmed osteoblastic bone metastases from solid organ cancer
- Pain not adequately controlled by conventional therapy

Strontium 89 or samarium 153 (Quadramet®) is considered **not medically necessary** when the above criteria are not met and for all other indications.

Note: Caution should be taken in patients with poor renal function and/or bone marrow function.

Rationale

Bone metastasis occurs when neoplastic cells migrate from a primary cancer to a distant bone. The most common primary cancers with a predilection for bone spread are breast, prostate, and lung cancer. Although no bone is exempt, highly vascular areas such as spine, pelvis, and femur are more susceptible to metastases. Bone metastasis can present as pain, fracture, or laboratory abnormalities. Treatment involves control of the underlying systemic cancer and local therapy such as surgery, radiation, and/or bone strengthening agents (bisphosphonates and RANKL monoclonal antibodies). Less frequently used therapies are the beta-emitting radionuclides: strontium 89 and samarium 153.

The FDA approved strontium 89 chloride in 1995 for the relief of bone pain in patients with painful skeletal metastases. In the landmark randomized phase III Canadian multicenter study that garnered strontium 89 FDA approval, patients (N = 126) with endocrine-refractory metastatic prostate cancer received local field radiotherapy and either strontium 89 or placebo. Progression of pain and tumor markers (prostate specific antigen, acid phosphatase, and alkaline phosphatase) response showed statistically significant differences between the arms in favor of strontium 89. A quality-of-life analysis demonstrated an overall statistical superiority of strontium-89 for alleviation of pain and improvement in physical activity; however, hematologic toxicity was greater in the strontium 89 group. In 2 separate randomized phase III trials, the addition of strontium 89 has been showed to improve symptom control and quality of life without

significant effect on overall survival.^{10, 11} Multiple additional open and controlled studies have reported the efficacy of strontium 89 in advanced prostate or breast cancer patients as well as other tumor types for pain relief.¹⁰⁻¹⁷

The FDA approved samarium 153 lexidronam (Quadramet®) in 1997 for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan. The results of 3 controlled studies have been reported. In the first prospective, multicenter, randomized, double-blind, placebo-controlled study (Study BA-106/110), patients (N = 180) with bone metastases from a variety of primary tumors were treated with single doses of placebo (N = 39) or active drug at doses of 0.5 mCi/kg (N = 40) or 1.0 mCi/kg (N = 39). Patients were followed for up to 16 weeks. The majority (86%) of the patients had either primary prostate (N = 80) or breast (N = 21) cancer. Patients who received the 1.0 mCi/kg dose of active drug had significant improvements when compared with the placebo group in both visual analog assessment scores and in the patient global assessment at each of the first 4 weeks following intervention. In the blinded patient global assessment, 62% to 72% of those in the 1.0 mCi/kg group and 40% to 70% of those in the 0.5 mCi/kg group had pain relief in the first 4 weeks following intervention. A significant correlation (P = .01) was observed between reductions in daily opioid analgesic use and visual analog assessment scores for patients receiving 1.0 mCi/kg.¹⁸

In another prospective, multicenter, randomized, double-blind, placebo-controlled study (Study 424Sm10/11), patients (N = 152) with bone metastases from hormone-refractory prostate cancer were randomized to placebo (N = 51) or 1.0 mCi/kg active drug (N = 101). As in the prior study, patients were followed for 16 weeks after intervention. Patients who received active drug had significant decreases in opioid analgesic use at weeks 3 and 4 (P < .0284). Changes in visual analog assessment scores were correlated with reductions in opioid analgesic use in the active treatment group (r = 0.349, P = .0004).¹⁹ Findings were further corroborated by another multicenter, randomized, single-blind, dose-controlled study of 114 patients with painful bone metastases from various primary tumors. A single dose of either 0.5 mCi/kg (N = 55) or 1.0 mCi/kg (N = 59) resulted in an improvement of physician's global assessment of 70% for the 1.0 mCi/kg group and 55% in the 0.5 mCi/kg group at week 4. Patients receiving the higher dose also exhibited significant improvements over baseline in both daytime discomfort and sleep at week 4. Long-term follow-up revealed a significantly longer survival among breast cancer patients receiving the higher dose; there was no correlation with survival and dose in the other tumor types.²⁰

Lymphoma

A single course of ibritumomab tiuxetan (Zevalin®) is considered **medically necessary** when **ANY** of the following conditions are met:

- Follicular B-cell CD20 positive non-Hodgkin lymphoma when **ALL** of the following conditions are met:
 - Individual is age 18 years or older
 - Relapsed or refractory disease, or after initial therapy when individual demonstrates a partial or complete response
 - Individual has adequate marrow reserve (cellularity > 15%, < 25% involvement of lymphoma, and platelets > 100,000 10⁹/L)
- Other low-grade B-cell CD20 positive non-Hodgkin lymphoma (such as marginal zone or MALT lymphoma) when **ALL** of the following conditions are met:
 - Individual is age 18 years or older
 - Relapsed or refractory disease
 - Individual has adequate marrow reserve (cellularity > 15%, < 25% involvement of lymphoma, and platelets > 100,000 10⁹/L)

Ibritumomab tiuxetan (Zevalin®) is considered **not medically necessary** when:

- The above criteria are not met
- Given as a repeat course of treatment
- Used as a part of a pre-transplant conditioning regimen
- Used for any other indication not included above

Rationale

Non-Hodgkin lymphoma is the seventh most common cancer in both men and women. Lymphomas are divided into Hodgkin and non-Hodgkin lymphomas. Non-Hodgkin lymphoma is further subdivided into indolent, aggressive, and highly aggressive. Aggressive and highly aggressive lymphomas generally present over weeks to months, while indolent lymphomas may be undiagnosed for years due to their slow rate of growth. Common presenting symptoms include enlarged lymph nodes, B symptoms (fevers, chills, night sweats, weight loss), or in the case of more aggressive non-Hodgkin lymphoma, symptoms resulting from local tumor growth or systemic metabolic derangements. The treatment for lymphoma typically involves chemotherapy, immunotherapy, and/or radiation. The FDA approved ibritumomab tiuxetan (Zevalin®) in 2002 for the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma or previously untreated follicular non-Hodgkin lymphoma who achieve a partial or complete response to first-line chemotherapy.

In the prospective, randomized, open-label, phase III (FIT) trial, 414 patients with stage III/IV, CD-20 positive, follicular lymphoma who achieved a complete or partial response to first-line induction therapy were randomized to treatment with ibritumomab tiuxetan vs no further treatment. The median progression-free survival for the ibritumomab-treated patients was 36.5 months vs 13.3 months with no additional treatment ($P < .0001$). After treatment with ibritumomab, 77% of patients with a partial response to chemotherapy achieved a complete response. Serious (grade 3 or 4) infections occurred in 8% of patients. A subsequent study with 7.3 years median follow-up reported a median time to next treatment of 8.1 years for the ibritumomab-treated patients compared to 3.0 years for the observation cohort ($P < .001$). As in the first report, there was no significant difference in overall survival. A noted limitation of the trial is that only 14% received rituximab during the induction phase.^{21,22}

In a single-arm, open-label phase II trial, patients ($N = 30$) with advanced, relapsed or refractory, low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma were treated with ibritumomab tiuxetan. The overall response rate was 83% (37% complete response, 6.7% complete response unconfirmed, and 40% partial response) with an estimated Kaplan-Meier median time to progression of 9.4 months (range, 1.7-24.6). As expected, the most commonly seen grade 4 toxicities were hematologic: neutropenia, thrombocytopenia, and anemia was 33%, 13%, and 3%, respectively.²³ In multicenter phase II trial, patients ($N = 143$) with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma were treated with ibritumomab tiuxetan or rituximab. Overall response rate was 80% ibritumomab tiuxetan vs 56% for the rituximab group ($P = .002$). Complete response rates were 30% and 16% in the ibritumomab tiuxetan and rituximab groups, respectively ($P = .04$). The time to progression was not statistically significant between the 2 arms and, although durable responses (64% vs 47%, $P = .030$) favored the ibritumomab tiuxetan arm. The most common grade 3/4 toxicities were myelosuppression.²⁴ Long-term follow-up of a phase I/II trial reported durable responses of over 2 years in patients who achieved complete response with ibritumomab tiuxetan, although the entire intention to treat population had a time to progression and duration of response of 12.6 months and 11.7 months, respectively.²⁵ In a review of 4 trials, the long term-outcomes of patients of 411 patients treated with yttrium 90 ibritumomab tiuxetan with recurrent or refractory B-cell non-Hodgkin lymphoma were reported. At a median follow-up of 53.5 months, the median duration of response was 28.1 months and the median time to progression was 29.3 months. The estimated overall survival at 5 years was 53% for all patients treated with 90Y ibritumomab tiuxetan and 81% for long-term responders. Results were comparable across non-Hodgkin lymphoma subtypes.²⁶

Several phase II trials have evaluated the use of ibritumomab tiuxetan as part of a pre-transplant conditioning regimen. One small randomized trial compared treatment with Y-90 ibritumomab tiuxetan plus BiCNU, etoposide, ara-C, melphalan (Z-BEAM) chemotherapy to treatment with BEAM alone before autologous stem cell transplantation in aggressive non-Hodgkin lymphoma. In this setting, adding ibritumomab tiuxetan to the pre-transplant regimen resulted in a non-significant increase in 2-year progression-free survival. This study was limited by low enrollment and was closed early due to poor accrual. The authors concluded that larger international studies with longer follow-up will be needed before ibritumomab tiuxetan can be accepted as a standard of care addition to the pre-transplant conditioning regimen.²⁷ In a retrospective study also using Z-BEAM prior to autologous stem cell transplant, patients ($N = 37$) with relapsed or refractory high-risk B-cell non-Hodgkin lymphoma reported a complete response in 59%, partial response in 27%, progressive disease in 11% and toxic death in 3%. After a median follow up of 61 months, the 3-year efficacy was not significant between the treatment arms: progression-free survival (57% vs 48%) and 3-year overall survival (60% vs 57%). In a subgroup analysis which included only 18 patients, an improvement in progression-free survival (78% Z-BEAM vs 22% BEAM, $P = .016$) and overall survival (83% Z-BEAM vs 22% BEAM, $P = .001$) was reported.²⁸ In a retrospective study of the EBMT Lymphoma Working Party, a multivariate analysis failed to show significant differences with Z-BEAM or R-BEAM compared with BEAM for incidences of relapse, non-relapse mortality, event-free survival, or overall survival.²⁹

Neuroendocrine Cancer

A single course of up to 4 planned injections of Lutetium Lu 177 dotatate (Lutathera®) is considered **medically necessary** for treatment of **EITHER**

- Locally advanced, inoperable or metastatic well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NET), including foregut, midgut and hindgut neuroendocrine tumors in adults

OR

- Locally advanced or metastatic bronchopulmonary and thymic neuroendocrine tumors when **ALL** of the following conditions are met:
 - Individual is age 18 years or older
 - An appropriate imaging study has been performed to document somatostatin receptor overexpression
 - Disease has progressed on at least 4 months of somatostatin receptor analog therapy and documented by radiographic imaging
 - Individual has an ECOG performance status of 0-2
 - Individual has not had prior treatment with a radiolabeled somatostatin analog

Lutetium Lu 177 dotatate (Lutathera®) is considered **not medically necessary** when:

- The above criteria are not met and for all other indications
- Given as a repeat course of treatment (*Note: A course can include up to 4 planned injections*)

Rationale

Neuroendocrine cancer is a rare type of cancer in which tumors arise from neuroendocrine cells, and may occur anywhere in the body. The most common neuroendocrine tumors are carcinoid tumors, the majority of which occur in the gastrointestinal tract. Well-differentiated neuroendocrine tumors often present with symptoms such as diarrhea, flushing, and wheezing due to excessive production of hormones whereas poorly differentiated tumors are classically nonsecretory and tend to cause symptoms related to local tumor growth or metastatic disease. Well-differentiated neuroendocrine cancers are classically treated with somatostatin analogs, chemotherapy, and targeted therapy. The FDA approved Lutetium Lu 177 dotatate in 2016 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 has been studied in the treatment of metastatic, well-differentiated neuroendocrine cancer in a randomized, phase III clinical trial (NETTER-1). The study randomized 229 patients with progressive, well-differentiated neuroendocrine cancers to best supportive care, including monthly octreotide long-acting repeatable therapy vs the same treatment plus 4 infusions of Lutetium Lu 177 dotatate given every 8 weeks. Tumors were either locally advanced, unresectable, or metastatic. At 20 months, the progression-free survival in the Lutetium Lu 177 dotatate patients was 65.2% vs 10.8% for the control group ($P < .001$). Response rates and overall survival were also higher in the Lutetium Lu 177 dotatate-treated patients. The most common adverse events were nausea and vomiting. Premedication with intravenous antiemetics is recommended. Serious adverse events were rare. Grade 3 or 4 neutropenia and thrombocytopenia were seen in 1%-2% of cases. Grade 3 or 4 lymphopenia was seen in 9% of cases. Before, during, and after Lutetium Lu 177 dotatate infusion, intravenous amino acids are given to protect the kidneys. No adverse renal events were reported.³⁰

In the Phase II (ERASMUS) trial, patients ($N = 1214$) with neuroendocrine tumors and positive ^{111}In -DTPA-octreotide scintigraphy were treated with Lutetium Lu 177 dotatate. A total of 610 patients were available for the safety analysis; 443 who had gastroenteropancreatic or bronchial neuroendocrine cancer and were treated with a cumulative dose of at least 600 mCi (22.2 GBq) of Lutetium Lu 177 dotatate before 2013 were assessed for the efficacy and survival analysis. The objective response rate of the total group of patients was 39%. Stable disease was reached in 43% of patients. Progression-free survival and overall survival for all neuroendocrine tumors patients were 29 months (95% CI, 26-33 months) and 63 months (95% CI, 55-72 months). Long-term toxicity included acute leukemia in 4 patients (0.7%) and myelodysplastic syndrome in (patients (1.5%). No therapy-related long-term renal or hepatic failure occurred.³¹

Pheochromocytoma and Paraganglioma

A single course of ^{131}I iobenguane (Azedra®) is considered **medically necessary** for treatment of adult and pediatric patients 12 years and older with pheochromocytoma or paraganglioma who require systemic anticancer therapy when **ALL** of the following conditions are met:

- Individual is age 12 years or older
- Iobenguane scan-positive
- Individual has an ECOG performance status of 0-2
- Patient has not received prior treatment with a radiolabeled somatostatin analog
- Unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma

^{131}I iobenguane (Azedra®) is considered **not medically necessary** when:

- The above criteria are not met
- Given as a repeat course of treatment
- Used for any other indication not included above

A single course of Lutetium ^{177}Lu dotatate is considered **medically necessary** for primary treatment of unresectable or metastatic pheochromocytoma or paraganglioma when **ALL** of the following conditions are met:

- Individual is age 18 years or older
- An appropriate imaging study has been performed to document somatostatin receptor overexpression
- Individual has an ECOG performance status of 0-2
- Patient has not received prior treatment with a radiolabeled somatostatin analog

Lutetium Lu 177 dotatate (Lutathera®) is considered **not medically necessary** when:

- The above criteria are not met
- Given as a repeat course of treatment (*Note: A course can include up to 4 planned injections*)
- Used for any other indication not included above

Rationale

Pheochromocytoma and paraganglioma are rare neuroendocrine cancers that arise from the chromaffin cells of the adrenal gland or extra-adrenal autonomic paraganglia. Hypersecretion of catecholamine often leads to hypertension, headaches, and sweating. Treatment of local disease classically has required resection or radiation therapy, while systemic disease is treated with chemotherapy. The FDA approved ¹³¹Iobenguane (Azedra®) in 2018 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. Lutetium ¹⁷⁷Lu dotatate has not been FDA approved for the treatment of pheochromocytoma or paraganglioma.

In an open-label, single-arm, multicenter phase II clinical trial (Study IB12B [NCT00874614]), patients (N = 81) 12 years and older with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma were treated with iobenguane I 131. Of 81 patients enrolled, 74 patients received a dosimetric dose of iobenguane I 131. Sixty-eight patients received 1 therapeutic dose (FA) and 50 received 2 as per protocol (PP). At study entry, 52% (35/68) had prior surgery and systemic therapy (I-131 MIBG and/or chemotherapy) for pheochromocytoma or paraganglioma. Greater than 50% tumor reduction occurred in 25% (95% CI, 16%-37%) of FA and 32% (95% CI, 21%-46%) of PP patients. The 12-month overall survival was 91% in FA patients and the median overall survival was 36.7 months (95% CI, 29.9-49.1). Survival was not affected by lung or liver metastases.³² Also included in the FDA review was the Phase II trial (Trial 1 [NCT01413503]) used for refinement of dosing and for evaluation of adverse events. The most common grade 3-4 adverse reactions (≥ 10%) were lymphopenia, neutropenia, thrombocytopenia, fatigue, anemia, increased international normalized ratio, nausea, dizziness, hypertension, and vomiting. In the pooled safety population, 6.8% of patients who received a therapeutic dose of iobenguane I 131 developed myelodysplastic syndrome or acute leukemia.²

In a 1997 review of 116 pheochromocytoma patients treated with ¹³¹I metaiodobenzylguanidine, Loh et al reported that initial symptomatic improvement was achieved in 76% of patients, tumor response in 30%, and hormonal response in 45%.³³ Additional smaller studies have resulted in similar findings.³⁴⁻³⁹ Objective response rates are approximately 30% with a larger proportion having stabilized disease. Limited evidence supports the use of larger doses (above 500mCi), and therefore should only be used in the setting of a clinical trial.^{34, 40}

In a small prospective trial, patients (N = 20) with unresectable paraganglioma/pheochromocytoma with high somatostatin receptor expression were treated with Lutetium Lu 177-dotatate. Fourteen patients were treated for uncontrolled hypertension and 6 for progressive or symptomatic metastatic disease or local recurrence. Three months after peptide receptor radionuclide therapy, 8 of 14 patients treated for HTN required reduced medication doses, 5 had no change in anti-HTN doses, and 1 was lost to follow-up. Eighty-six percent had serum chromogranin-A reduction. Of the entire cohort, 36% had disease regression (29% partial and 7% minor response) on computed tomography, with stable findings in 50%. Three other patients had bony disease evaluable only on somatostatin receptor imaging (2 partial response and 1 stable). Median progression-free survival was 39 months; median overall survival was not reached (5 deaths; median follow-up, 28 months). Grade 3 or 4 adverse events included lymphopenia in 4 patients and thrombocytopenia in 2 patients.⁴¹

Prostate Cancer

A single course of Radium 223 (Xofigo®) as monotherapy, up to 6 planned monthly injections, is considered **medically necessary** for treatment of prostate cancer when **ALL** of the following conditions are met:

- Individual is age 18 years or older
- Individual has a good performance status (ECOG 0-2)
- Metastatic, castrate-resistant prostate cancer
- Serum testosterone level is less than 50 ng/dl
- Symptomatic bone metastases only, with no visceral involvement
- No bulky (>3 cm) lymph node metastases
- Disease is worsening or progressing and **ANY** of the following conditions are met:
 - Based on imaging demonstrating worsening bone metastases
 - Based on PSA over 5 ng/mL and rising over 2 consecutive lab evaluations

Radium 223 (Xofigo®) is considered **not medically necessary** when:

- The above criteria are not met and for all other indications
- Given as a repeat course of treatment

- Systemic radiotherapy with radioisotopes given within the previous 24 weeks
- Chemotherapy or biologic therapy given within the previous 4 weeks
- Used concurrently with docetaxel or any other systemic therapy except androgen deprivation therapy (ADT)
- Used in combination with abiraterone acetate (Zytiga®) plus prednisone or prednisolone
- There is evidence of spinal cord compression

Rationale

Prostate cancer is the most common malignancy among men in the U.S.⁴² Patients most commonly present with asymptomatic elevation in PSA, abnormal prostate exam, urinary symptoms (urgency, frequency, and nocturia), hematuria, and occasionally bone pain if skeletal metastases are present. The treatment of prostate cancer is dependent on life expectancy and risk. For patients with localized disease, both radiation therapy and radical prostatectomy may be used as definitive treatment. The clinician may endorse additional hormone therapy based on pre-treatment or surgical findings. For patients with disseminated disease, an array of different hormone-manipulating medications or chemotherapy is available. For select patients, immunotherapy or radioactive radium-223 can also be used.

In the double-blind, placebo-controlled phase III (ALSYMPCA) trial, patients (N = 921) who had received, were not eligible to receive, or declined docetaxel were randomized 2:1 to receive 6 injections of radium-223 (at a dose of 50 kBq per kilogram of body weight intravenously) or matching placebo. At the interim analysis, which included 809 patients, radium-223, as compared with placebo, significantly improved overall survival (median, 14.0 months vs 11.2 months; hazard ratio, 0.70; 95% CI, 0.55-0.88; two-sided P = .002). The updated analysis of 921 patients confirmed the radium-223 survival benefit (median, 14.9 months vs 11.3 months; hazard ratio, 0.70; 95% CI, 0.58-0.83; P < .001). Assessments of all main secondary efficacy end points also showed a benefit of radium-223 as compared with placebo. Subgroup analysis showed that survival benefit was seen regardless of prior docetaxel use as well as improvement in quality-of-life and disease-related events.⁴³⁻⁴⁵ Final long-term safety analysis of ALSYMPCA showed radium-223 was well tolerated with low myelosuppression incidence and no new safety concerns.⁴⁶

Two separate trials have shown that radium-223 may be safely combined with abiraterone or enzalutamide. In a phase I/IIa study, the combination of docetaxel and Radium-223 in castrate resistant prostate cancer patients with ≥ 2 bone metastases also appears to be safe and effective in reducing biochemical markers.⁴⁷ In contrast, a double-blind, placebo-controlled randomized phase III trial assessing 806 patients with asymptomatic/mildly symptomatic chemotherapy-naive mCRPC and bone metastases treated with abiraterone acetate and prednisone/prednisolone (AAP) +/- Ra-223 reported worsened median SSE-FS and mOS in the group treated with AAP and Radium-223: 22.3 mo (95% CI, 20.4-24.8) vs 26.0 mo (95% CI, 21.8-28.3) (HR 1.122, 95% CI, 0.917-1.374; P = .2636) and 30.7 mo (95% CI, 25.8-not estimable) vs 33.3 mo (95% CI, 30.2-41.1) (HR 1.195, 95% CI, 0.950-1.505; P = .1280), respectively. Fractures were also seen in 29% in the combination arm and only 11% in the AAP arm.⁴⁸

Thyroid Cancer

Radioactive iodine 131 is considered **medically necessary** for differentiated thyroid cancer when **ANY** of the following conditions are met:

- Definitive treatment for low-risk patients when surgery is not planned (e.g., due to patient comorbidities or refusal)
- Adjuvant treatment after total thyroidectomy/partial thyroidectomy (except in low-risk patients)
- Treatment of unresectable gross residual disease after total thyroidectomy/partial thyroidectomy
- Treatment of known or suspected metastatic disease and radioiodine-avid thyroid scintigraphy
- Treatment of persistent disease found on post radioactive iodine therapy imaging
- Treatment of suspected recurrence based on biochemical testing

Radioactive iodine 131 is considered **not medically necessary** when the above criteria are not met and for all other indications.

Repeat I-131 should be limited to patients with prior response to radioactive iodine treatment. Repeat treatment should not occur sooner than 6 to 12 months following prior treatment.

Refer to inpatient medical policy for sodium iodide I-131 for full coverage details.

Table 1: Common features of low-risk thyroid cancer

Low-risk papillary thyroid cancer	Low-risk follicular and hurthle cell thyroid cancer
Classic papillary thyroid cancer	-
Largest primary tumor < 2 cm	Largest primary tumor < 2 cm
Intrathyroidal	Intrathyroidal
Unifocal or multifocal (all foci < 1 cm)	No vascular invasion
No detectable anti-Tg antibodies	Clinical NO
Postoperative unstimulated Tg < 1 ng/mL	Postoperative unstimulated Tg < 1 ng/mL

Rationale

Thyroid cancer is the most common endocrine cancer in the U.S. The most common histologies are papillary thyroid carcinoma and follicular carcinoma, which account for 95% of all thyroid cancers. Most patients with differentiated thyroid cancer will undergo thyroidectomy. Radioactive iodine can be used for imaging and/or treatment of differentiated thyroid cancers. Thyroid stimulating hormone suppression, external beam radiation therapy, and small molecule multikinase inhibitors are often also employed for the treatment of recurrent, residual, or metastatic disease. In 1971, the FDA approved sodium iodide I 131, a radioactive therapeutic agent, for the treatment of hyperthyroidism and thyroid carcinomas that take up iodine. I 131 has typically been used in 3 distinct scenarios: complete ablation of remnant thyroid, adjuvant treatment for high-risk disease, and treatment of persistent/metastatic disease.

In a review by the American and European Thyroid Associations, patients (N = 1298) with low-risk differentiated thyroid cancer treated with radioactive iodine were evaluated. Ten-year overall survival was found to be 95.8% in patients without radioactive iodine treatment after surgery vs 94.6% in patients with radioactive iodine treatment after surgery and 10-year disease-free survival was found to be 93.1% vs 88.7% (P = .001). Using multivariate Cox analyses, radioactive iodine was neither significantly nor independently associated with overall survival (P = .243) and disease-free survival (P = .2659).⁴⁹ Multiple systematic reviews and meta-analyses have also failed to show conclusive benefit for treatment of Stage I and/or low-risk disease.⁵⁰⁻⁵⁵ A rise in salivary gland malignancies (SIR = 11.13; 95% CI, 1.35-40.2) and leukemia (SIR = 5.68; 95% CI, 2.09-12.37) has also been reported with I 131 therapy. The risk of leukemia was significantly greater in patients aged < 45 years (SIR = 5.32; 95% CI, 2.75-9.30) compared with the risk in older patients (SIR = 2.26; 95% CI, 1.43-3.39).⁵⁶

The use of I 131 in the intermediate to high-risk differentiated thyroid cancer population has been shown to decrease recurrence as well as improve disease-specific mortality. In patients with tumors > 1.5cm, fewer cancer deaths occurred after thyroid remnant ablation than after other treatment strategies (P < .001).⁵³ In a review of the NCI database of 21,870 patients with intermediate-risk papillary carcinoma who underwent total thyroidectomy with or without radioactive iodine, improvement in overall survival was seen in all patients (P < .001) as well as a 29% reduction in the risk of death, with a hazard risk of 0.71 (95% CI, 0.62-0.82, P < .001).⁵⁷ In a multicenter study, patients (N = 395) with high-risk differentiated thyroid cancer had an improvement in overall mortality (RR 0.17; 95% CI, 0.06-0.47), cancer-specific mortality (RR 0.12; 95% CI, 0.04-0.42), progression (RR 0.21; 95% CI, 0.08-0.56), and disease-free survival (RR 0.29; 95% CI, 0.08-1.01).⁵⁸ In an NTCTCS Registry analysis of 491 patients, stage III patients who received radioactive iodine (RR 0.66; P = .04) and stage IV patients who received both total/near-total thyroidectomy and radioactive iodine (RR, 0.66 and 0.70; combined P = .049) also had an improved overall survival.⁵⁹ In a review of the SEER data base, multivariate analysis failed to show radioactive iodine significantly affecting mortality (P = .9176). Subgroup analysis identified patients older than 45 years with primary tumors > 2 cm and disease in the lymph nodes with distant metastatic disease as the only group positively affected by radioactive iodine.⁶⁰ A smaller study that exclusive included patients with metastatic thyroid cancer, the risk of recurrence was 7% for patients who achieved resolution of the radioiodine-avid metastatic lesions. Overall survival at 10 years after initiation of I 131 treatment was 92% in patients who achieved a negative study and 19% in those who did not.⁶¹

Codes

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The following code list is not meant to be all-inclusive. Authorization requirements will vary by health plan. Please consult the applicable health plan for guidance on specific procedure codes.

Specific CPT codes for services should be used when available. Nonspecific or not otherwise classified codes may be subject to additional documentation requirements and review.

Ibritumomab tiuxetan (Zevalin®)

CPT/HCPCS

A9543..... Yttrium Y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 millicuries
79403 Radiopharmaceutical therapy, radiolabeled monoclonal antibody by intravenous infusion

ICD-10 Diagnoses

C81.00 - C88.9 Lymphoma
C82.00 - C82.99 ... Nodular lymphoma (or follicular)
C83.80 - C83.89 ... Other named variants of lymphosarcoma and reticulosarcoma
C83.90 - C88.9 Other malignant lymphomas
C88.4..... Marginal zone lymphoma (MALT)

Iobenguane I 131 (Azedra®)

CPT/HCPCS

A9590..... Iodine i-131, iobenguane, 1 millicurie
79101 Radiopharmaceutical therapy, by intravenous administration

ICD-10 Diagnoses

C74.00 - C74.92 ... Malignant neoplasm of adrenal gland [paragangliomas, pheochromocytomas]
C7A.00 - C7A.8 Malignant carcinoid tumors
D35.00 - D35.02 ... Benign neoplasm of adrenal gland [paragangliomas, pheochromocytomas]

Lutetium Lu 177-dotatate (Lutathera®)

CPT/HCPCS

A9513..... Lutetium lu 177, dotatate, therapeutic, 1 millicurie
A9699..... Radiopharmaceutical therapy, not otherwise classified
79101 Radiopharmaceutical therapy, by intravenous administration

ICD-10 Diagnoses

C25.4..... Malignant neoplasm of endocrine pancreas
C74.10 - C74.12 ... Malignant neoplasm of medulla of adrenal gland
C74.90 - C74.92 ... Malignant neoplasm of unspecified part of adrenal gland
C75.5..... Malignant neoplasm of aortic body and other paraganglia
C7A.00 - C7A.8 Malignant carcinoid tumors
C7B.00 - C7B.09 .. Secondary carcinoid tumors
C7B.8 Other secondary neuroendocrine tumors
E34.0..... Carcinoid syndrome
Z85.020 Personal history of malignant carcinoid tumor of stomach
Z85.030 Personal history of malignant carcinoid tumor of large intestine
Z85.040 Personal history of malignant carcinoid tumor of rectum
Z85.060 Personal history of malignant carcinoid tumor of small intestine
Z85.07 Personal history of malignant neoplasm of pancreas
Z85.110 Personal history of malignant carcinoid tumor of bronchus and lung
Z85.230 Personal history of malignant carcinoid tumor of thymus
Z85.858 Personal history of malignant neoplasm of other endocrine glands

Radium (Ra)-223 dichloride (Xofigo®)

CPT/HCPCS

A9606..... Radium ra-223 dichloride, therapeutic, per microcurie
 79101 Radiopharmaceutical therapy, by intravenous administration

ICD-10 Diagnoses

C61..... Malignant neoplasm of prostate
 C79.51..... Secondary malignant neoplasm of bone
 R97.21..... Rising PSA following treatment for malignant neoplasm of prostate
 Z19.2..... Hormone resistant malignancy status

Samarium Sm 153 lexidronam (Quadramet®)

CPT/HCPCS

A9604..... Samarium sm-153 lexidronam, therapeutic, per treatment dose, up to 150 millicuries
 A9605..... Samarium sm-153 lexidronam, therapeutic, per 50 millicuries

ICD-10 Diagnoses

C61..... Malignant neoplasm of prostate
 C79.51..... Secondary malignant neoplasm of bone
 R97.21..... Rising PSA following treatment for malignant neoplasm of prostate
 Z19.2..... Hormone resistant malignancy status

Sodium iodide I 131

CPT/HCPCS

A9528 Iodine i-131 sodium iodide capsule(s), diagnostic, per millicurie
 A9531 Iodine i-131 sodium iodide, diagnostic, per microcurie (up to 100 microcuries)
 78012 Thyroid uptake, single/multiple quantitative measurement(s)
 78013 Thyroid imaging with vascular flow
 78014 Thyroid uptake w/blood flow, single/multiple quantitative measurement(s)
 78015 Thyroid carcinoma metastases imaging, limited area
 78016 Thyroid carcinoma metastases imaging, additional study
 78018 Thyroid carcinoma metastases imaging whole body
 79005 Radiopharmaceutical therapy, by oral administration

ICD-10 Diagnoses

Refer to the ICD-10 CM manual
 C73..... Malignant neoplasm of the thyroid gland

Strontium Sr 89 chloride

CPT/HCPCS

A9600..... Strontium sr-89 chloride, therapeutic, per millicurie

ICD-10 Diagnoses

C61..... Malignant neoplasm of prostate
 C79.51..... Secondary malignant neoplasm of bone
 R97.21..... Rising PSA following treatment for malignant neoplasm of prostate
 Z19.2..... Hormone resistant malignancy status

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History

Status	Review Date	Effective Date	Action
Revised	05/26/2021	03/13/2022	Independent Multispecialty Physician Panel (IMPP) review. Added patient requirements for treatment of bronchopulmonary and thymic NETs with lutetium Lu 177 dotatate, and for treatment of pheochromocytoma and paraganglioma with either lutetium Lu 177 dotatate or 131I iobenguane. Added exclusion for radium 223 when used in combination with abiraterone acetate for prostate cancer.
Revised	05/26/2021	11/07/2021	IMPP review. Removed requirement for disease progression for locally advanced, inoperable or metastatic well-differentiated somatostatin receptor-positive GEP-NETs, including foregut, midgut and hindgut NETs in adults. Removed Metastron as brand no longer manufactured. Updated references.
Revised	07/08/2020	03/14/2021	IMPP review. Added CPT code 79005; removed A9508, 78800, 78801, 78802, 78803, 78804.
Revised	05/11/2020	03/14/2021	IMPP review. Revised criteria for Zevalin for non-Hodgkin lymphoma and Xofigo for prostate cancer.
Created	03/25/2019	06/01/2020	IMPP review. Original effective date.