Medical Policy
Therapeutic Radiopharmaceuticals in Oncology

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Policy Number: 028
BCBSA Reference Number: 6.01.60
NCD/LCD: N/A

Related Policies
Therapeutic Radiopharmaceuticals in Oncology for the Treatment of Gastroenteropancreatic, Bronchopulmonary, and Thymus Neuroendocrine Tumors (LUTETIUM 177 DOTATATE) Prior Authorization Request Form, #958

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

Prior Authorization Request Form: Therapeutic Radiopharmaceuticals in Oncology
This form must be completed and faxed to: Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.
- Click here for Therapeutic Radiopharmaceuticals in Oncology for the Treatment of Gastroenteropancreatic, Bronchopulmonary, and Thymus Neuroendocrine Tumors (LUTETIUM 177 DOTATATE) Prior Authorization Request Form, #958

LUTETIUM 177 (LU 177) DOTATATE

INITIAL TREATMENT
Lutetium 177 (Lu 177) dotatate treatment is considered MEDICALLY NECESSARY when conditions 1 through 8 are met:
1. Patient is an adult (≥18 years of age).
2. Patient has documented low or intermediate grade (Ki-67 index ≤20%), locally advanced or metastatic, gastroenteropancreatic (including foregut, midgut, and hindgut) or bronchopulmonary or thymus neuroendocrine tumor.
3. Patient has documented somatostatin receptor expression of a neuroendocrine tumor as detected by somatostatin receptor–based imaging (68Ga-dotate positron emission tomography or computed tomography, which is preferred) or somatostatin receptor scintigraphy.
4. Patient has documented disease progression while on octreotide long-acting release therapy.
5. Patient is not receiving long-acting somatostatin analogues for at least 4 weeks prior to initiating Lu 177 dotatate.
6. Patients does not have severe renal impairment (creatinine clearance, <30 mL/min).
7. Patient has adequate bone marrow and hepatic function as determined by the treating physician.
8. Patient has documented Karnofsky Performance Status score of 60 or greater.

CONTINUATION OF TREATMENT
Continuation of Lu 177 dotatate is considered MEDICALLY NECESSARY when conditions 1 through 5 are met:
1. No recurrent grade 2, 3, or 4 thrombocytopenia (see Table PG1).
2. No recurrent grade 3 or 4 anemia and neutropenia (see Table PG1).
3. No recurrent hepatotoxicity*
4. No recurrent grade 3 or 4 nonhematologic toxicity (see Table PG1).
5. Renal toxicity requiring a treatment delay of 16 weeks or longer.*

Lu 177 dotatate treatment is considered INVESTIGATIONAL in all other situations in which the above criteria are not met.

Lu 177 dotatate treatment greater than a total of 4 doses as per the Food and Drug Administration–approved regimen is considered INVESTIGATIONAL.

*Lu 177 dotatate should be discontinued permanently if the patient develops hepatotoxicity defined as bilirubinemia greater than 3 times the upper limit of normal (grade 3 or 4), or hypoalbuminemia less than 30 g/L with a decreased prothrombin ratio less than 70%.

**Lu 177 dotatate should be discontinued permanently if patient develops renal toxicity defined as a creatinine clearance of less than 40 mL/min calculated using Cockcroft-Gault equation with actual body weight, or 40% increase in baseline serum creatinine, or 40% decrease in baseline creatinine clearance calculated using Cockcroft-Gault equation with actual body weight.

Table 1 describes the grading of severity used in the Common Toxicity Criteria for Adverse Events (version 4.03).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living and refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.</td>
</tr>
<tr>
<td>3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living and refer to refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>5</td>
<td>Death related to adverse event.</td>
</tr>
</tbody>
</table>

IOBENGUIANE I-131

Iobenguane I-131 is considered MEDICALLY NECESSARY when conditions 1 through 5 are met:
1. Patient has documented iobenguane scan positive, locally advanced or metastatic pheochromocytoma and paraganglioma.
2. Patient is 12 years or older.
3. Patient has progressed on prior therapy for pheochromocytoma or paraganglioma OR is not a candidate for chemotherapy.
4. Patient does not have severe renal impairment (creatinine clearance <30 mL/min).
5. Patient has platelet count greater than 80,000/mcL OR absolute neutrophil count greater than 1,200/mcL.

Iobenguane I 131 treatment is considered INVESTIGATIONAL for all other indications including neuroblastoma and gastroenteropancreatic neuroendocrine tumors.

Use of iobenguane I 131 not in accordance with FDA approved dosing (first dosimetric dose followed by two therapeutic doses administered 90 days apart*) is considered INVESTIGATIONAL.

*Iobenguane I 131
- Iobenguane I 131 is administered intravenously as a dosimetric dose followed by two therapeutic doses administered 90 days apart.
  - The recommended dosimetric dose is 185 to 222 MBq (5 to 6 mCi) in patients greater than 50 kg and 3.7 MBq/kg (0.1 mCi/kg) in patients 50 kg or less.
  - The recommended therapeutic dose is 18,500 MBq (500 mCi) in patients greater than 62.5 kg and 296 MBq/kg (8 mCi/kg) in patients 62.5 kg or less.
- Thyroid-blocking medications should be given prior to administration and after each dose.
- Iobenguane I 131 is a radiopharmaceutical and should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.
- Iobenguane I 131 should be discontinued if
  - Platelet count is less than 80,000 mcL or absolute neutrophil count (ANC) is less than 1,200/mcL.
  - Patient has liver dysfunction defined as aspartate aminotransferase or alanine aminotransferase ≥ 2.5 times the upper limit of normal or total bilirubin > 1.5 times the upper limit of normal or develops liver disease (including hepatitis and chronic alcohol abuse).
  - Patient develops renal toxicity defined as a creatinine clearance of < 30 mL/min.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th></th>
</tr>
</thead>
</table>
| Commercial Managed Care (HMO and POS) | Prior authorization is **required** for Lutetium 177 dotatate.*
|            | Prior authorization is **not required** for Iobenguane I-131. |
| Commercial PPO and Indemnity | Prior authorization is **required** for Lutetium 177 dotatate.*
|            | Prior authorization is **not required** for Iobenguane I-131. |
| Medicare HMO Blue℠ | Prior authorization is **required** for Lutetium 177 dotatate.*
|            | Prior authorization is **not required** for Iobenguane I-131. |
| Medicare PPO Blue℠ | Prior authorization is **required** for Lutetium 177 dotatate.*
|            | Prior authorization is **not required** for Iobenguane I-131. |

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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A9513</td>
<td>Lutetium lu 177, dotatate, therapeutic, 1 millicurie</td>
</tr>
<tr>
<td>A9590</td>
<td>Iodine i-131, iobenguane, 1 millicurie</td>
</tr>
</tbody>
</table>

Description

Neuroendocrine tumors

Neuroendocrine tumors are a heterogeneous group of tumors that originate from the neuroendocrine cells in the diffuse neuroendocrine system anywhere in the body but more commonly in the gastrointestinal tract and the respiratory system. Approximately 61% of all neuroendocrine tumors originate from the gastrointestinal system or pancreas and are referred to as gastroenteropancreatic neuroendocrine tumors. Lung neuroendocrine tumors may also be referred to as pulmonary neuroendocrine tumors, pulmonary carcinoids, or bronchopulmonary neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors may further be characterized as functional or nonfunctional based on whether they secrete hormones that result in clinical symptoms particularly serotonin, which results in "carcinoid syndrome" that is characterized by flushing and diarrhea.

Neuroendocrine tumors are classified as orphan diseases by the Food and Drug Administration (FDA). Based on an analysis of Surveillance, Epidemiology, and End Results Program registry data from 1973 to 2012, the overall incidence of neuroendocrine tumors has been reported to be in the range of 6.98 per 100000 people per year.1

Diagnosis

Neuroendocrine tumors are not easy to diagnose because of the rarity of the condition. Symptoms are often nonspecific or mimic other disorders such as irritable bowel syndrome (in the case of gastroenteropancreatic neuroendocrine tumors) or asthma (in the case of a lung neuroendocrine tumors) resulting in an average diagnosis delay of five to seven years after symptom onset.2 In many cases, diagnosis is incidental to imaging for other unrelated cause. Most gastroenteropancreatic neuroendocrine tumors express somatostatin receptors that can be imaged using a radiolabeled form of the somatostatin analogueoctreotide (eg, 111In pentetreotide).

Treatment Approach

There is a general lack of prospective data to guide the treatment of neuroendocrine tumors. Gastroenteropancreatic neuroendocrine tumors are chemotherapy-responsive neoplasms, and platinum-based chemotherapy represents the backbone of treatment for both early and advanced-stage tumors.3 Surgery alone or followed by chemotherapy along with treatment of hormone-related symptoms...
may be the initial approach for localized disease. For asymptomatic patients with slow progression, observation with routine surveillance imaging is an option. The prognosis for patients with metastatic welldifferentiated gastroenteropancreatic neuroendocrine tumors is highly variable. Based on retrospective analyses of large databases, the prognosis for patients with metastatic gastroenteropancreatic neuroendocrine tumors is variable. The median overall survival (from diagnosis) for patients with metastatic pancreatic neuroendocrine tumors has been reported to range from 2 to 5.8 years[4] while the median overall survival for small bowel neuroendocrine tumors has been reported as 7.9 years.5

Pharmacologic Treatment
First-Line Treatment Options
Somatostatin Analogues (Octreotide and Lanreotide)
Somatostatin is a peptide that binds to somatostatin receptors that are expressed in a majority of carcinoid tumors and inhibits the secretion of a broad range of hormones. Somatostatin analogues (eg, octreotide, lanreotide) were initially developed to manage the hormonal symptoms related to neuroendocrine tumors, they were found to exert antiproliferative activity, and clinical studies have demonstrated prolonged progression-free survival (PFS) in patients with neuroendocrine tumors treated with somatostatin analogues.6,7 However, the role of somatostatin analogues in patients with nonfunctioning neuroendocrine tumors is unclear.8

Commercially available long-acting release forms of octreotide and lanreotide (eg, Sandostatin LAR, Somatuline Depot), which are administered intramuscularly on a monthly basis, have largely eliminated the need for daily self-injection of short-acting subcutaneous formulations.9,10

Second-Line Treatment Options
Currently, there are no data to support a specific sequence of therapies and only streptozocin, everolimus, and sunitinib are FDA approved for the treatment of pancreatic neuroendocrine tumors.

Mechanistic Target of Rapamycin Inhibitors
The mechanistic target of rapamycin is an enzyme that regulates cell metabolism and proliferation in response to environmental stimuli. It is upregulated in a variety of malignancies in response to stimulation by growth factors and cytokines. Whole-exome genomic analysis has shown that approximately 15% of pancreatic neuroendocrine tumors are associated with somatic variants in genes associated with the mechanistic target of rapamycin pathway.11

Everolimus, an oral mechanistic target of rapamycin inhibitor, has been shown to significantly prolonged PFS vs placebo in patients with pancreatic neuroendocrine tumors (RADIANT-3 trial),12 and lung and gastrointestinal neuroendocrine tumors nonfunctional (RADIANT-4 trial).12 Note that everolimus is approved by the FDA for adults with progressive neuroendocrine tumors of pancreatic origin and adults with progressive, well-differentiated, nonfunctional neuroendocrine tumors of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic. The RADIANT-2 trial patients with progressive advanced neuroendocrine tumors associated with carcinoid syndrome failed to show a statistically significant improvement in the primary endpoint of PFS.14

Tyrosine Kinase Receptor Inhibitors
Neuroendocrine tumors frequently overexpress the vascular endothelial growth factor and receptor. Sunitinib is a multi-targeted tyrosine kinase inhibitor that targets multiple signaling pathways and growth factors and receptors including vascular endothelial growth factor and receptor 1, 2, and 3.11

It has been shown that daily sunitinib at a dose of 37.5 mg improves PFS, overall survival, and the overall response rate as compared with placebo among patients with advanced pancreatic neuroendocrine tumors.15

Note that sunitinib is FDA approved for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.
**Chemotherapy**
Response to chemotherapy for advanced neuroendocrine tumors of the gastrointestinal tract and lung is highly variable and, at best, modest. Tumor response rates are generally low and no PFS benefit has been clearly demonstrated. Therefore, the careful selection of patients is critical to maximize the chance of response and avoid unnecessary toxicity. In advanced neuroendocrine tumors, platinum-based regimens are generally used. They include cisplatin and etoposide (most widely used), carboplatin and etoposide, 5-fluorouracil, capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide.\(^{16}\)

**Lutetium 177 Dotatate**
Lutetium 177 dotatate is a radiolabeled-somatostatin analogue that binds to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors. It is then internalized and beta particle emission from lutetium 177 induces cellular damage by formation of free radicals in somatostatin receptor-positive and neighboring cells.

**Pheochromocytoma and Paraganglioma**
Pheochromocytoma and paraganglioma are rare neuroendocrine tumors that originate from the chromaffin cells of the adrenal glands.\(^{17}\)

Chromaffin cells produce catecholamine neurotransmitters, such as epinephrine, norepinephrine, and dopamine. Compared to the normal chromaffin cells, pheochromocytomas and paraganglioma express high levels of the norepinephrine transporter on their cell surfaces. The excess amount of norepinephrine causes the clinical signs and symptoms like hypertension, headache, sweating, tremor, and palpitation. While most pheochromocytoma and paraganglioma are non-malignant (non-metastatic), about 10% of pheochromocytoma are malignant and about 25% of paraganglioma are malignant (metastatic) which can spread to other parts of the body, such as the liver, lungs, bone, or distant lymph nodes.\(^{18}\)

The average age of diagnosis is 43 years old. The estimated annual incidence of pheochromocytoma and paraganglioma is approximately 1 in 300000 population.\(^{19}\)

The 5-year mortality rates for patients with metastatic pheochromocytoma and paraganglioma has been reported as 37% depending on the primary tumor site and sites of metastases.\(^{20}\)

In addition, the medical overall and disease-specific survival were 24.6 and 33.7 years for pheochromocytoma and paraganglioma.\(^{21}\)

**Diagnosis**
The initial diagnosis of pheochromocytomas and paragangliomas includes biochemical testing, such as blood tests and urinalysis which measure the levels of metanephrine, a catecholamine metabolite in blood and urine. Imaging may be used to detect the location and size of tumors within the organs or tissues. Other advanced diagnostic procedures, such as \(^{123}\)I-metaiodobenzylguanidine (MIBG) scintigraphy, octreotide scan, and fluorodeoxyglucose-positron emission tomography scan are used to further determine whether the tumors are malignant and metastatic.\(^{17}\)

Certain genetic disorders such as multiple endocrine neoplasia 2 syndrome, von Hippel-Lindau syndrome, Neurofibromatosis type 1, hereditary paraganglioma syndrome\(^{22}\) are considered risk factors for pheochromocytomas and paragangliomas and therefore genetic testing is recommended for all patients with pheochromocytoma or paraganglioma.\(^{17}\)

**Treatment Approach**
Surgical resection is mostly reserved for benign tumors as curative surgical resection is nearly impossible in metastatic disease. For patients with local, unresectable disease, palliative external beam radiotherapy may be used with or without cytoreductive resection for patients with bone metastases.\(^{22}\)

Prior to the approval of lobenguane I 131, there was no FDA approved therapies for this indication. Radiotherapy options include off-label use of I 131-metaiodobenzylguanidine (\(^{131}\)I-MIBG) for patients with
MIBG-positive tumors.\textsuperscript{12} \textsuperscript{131}I-MIBG contains radioactive iodine and the compound is structurally similar to norepinephrine. When \textsuperscript{131}I-MIBG is delivered to the target tissue, it gives off beta-radiation killing neuroendocrine tumors. Due to the nature of the radiopharmaceutical mechanism of action, \textsuperscript{131}I-MIBG can cause toxicities including nausea, vomiting, anemia, leukocytopenia, and thrombocytopenia. There is limited evidence for chemotheraphy. In the case of unresectable progressive pheochromocytoma or paraganglioma, combination use of cyclophosphamide, dacarbazine, vincristine, doxorubicin, temozolomide, and thalidomide have been used.\textsuperscript{24} Tyrosine kinase receptor inhibitors such as sunitinib have also been used.\textsuperscript{26}

**Summary**

Radiopharmaceuticals are composed of a radioisotope bond to an organic molecule and are used for diagnostic and therapeutic purposes. The organic molecule conveys the radioisotope to specific organs, tissues, or cells. Lutetium 177 (Lu 177) dotate, classified as peptide receptor radionuclide therapy is a radiolabeled-somatostatin analogue that binds to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors such as neuroendocrine tumors. It is then internalized and beta particle emission from Lu 177 induces cellular damage by formation of free radicals in somatostatin receptor-positive and neighboring cells. Similar to Lu 177, iobenguane I 131 is a radioactive therapeutic agent, which is similar in structure to norepinephrine. Due to its structural similarity with norepinephrine, iobenguane is taken up by the norepinephrine transporter where it accumulates in adrenergically innervated tissues including pheochromocytoma and paraganglioma cells. The beta and gamma radiation resulting from the radioactive decay causes an anti-tumor affect.

For individuals with a treatment-refractory gastroenteropancreatic neuroendocrine tumor including foregut, midgut, and hindgut tumors who receive Lu 177 dotate, the evidence includes a randomized, open-labeled trial and a retrospective cohort study. The relevant outcomes are overall survival (OS), disease-specific survival, quality of life, and treatment-related mortality and morbidity. The randomized controlled trial results showed a consistent statistically significant and clinically meaningful effect on overall response rate, progression-free survival, and overall survival among patients treated with Lu 177 dotate compared to those treated with long-acting octreotide. The results of the retrospective cohort study were consistent with the treatment effect observed in the randomized controlled trial and provide additional support for a clinical benefit of Lu 177 dotate in patients with a gastroenteropancreatic neuroendocrine tumor. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a treatment-refractory bronchopulmonary or thymus neuroendocrine tumors who receive Lu 177 dotate, the evidence includes a retrospective cohort study. The relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The retrospective cohort study included a small number of patients with bronchopulmonary (n=23) or thymus (n=2) neuroendocrine tumors. Among the 23 patients with bronchopulmonary neuroendocrine tumor, the median progression-free survival was 20 months, the median time to progression was 25 months, and median overall survival was 52 months. Stratified results of two patients with thymus neuroendocrine tumors were not reported. The Food and Drug Administration in its review of the ERASMUS study for patients with gastroenteropancreatic neuroendocrine tumor concluded that time to event analyses such as time to progression, progression-free survival, and OS were not interpretable in the context of the single-arm ERASMUS study because of missing data at baseline, high dropout rates and open-label design of the study. Of note, despite the current evidence base, National Comprehensive Cancer Network guidelines give a category 2A recommendation for use of Lu 177 dotate for the treatment of bronchopulmonary and thymic locoregional advanced or distant metastases neuroendocrine tumors if there are clinically significant tumor burden and low grade (typical) or evidence of progression or intermediate grade (atypical). The evidence is insufficient to determine the effects of technology on health outcomes.

For individuals with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticaner therapy and who receive iobenguane I 131, the evidence includes a single-arm prospective cohort study. The relevant outcomes include OS, disease-specific survival, quality of life, treatment-related mortality and morbidity. The pivotal study reported that 25% of patients (95%
confidence interval 16.2% to 36.5%) met the primary endpoint of reduction in antihypertensive medication of at least 50% for at least 6 months along with 22.1% of patients having a confirmed, centrally reviewed partial response (95% confidence interval: 13.6% to 32.7%). Of these, 53% of patients who responded to therapy maintained a duration of response for at least 6 months. The single-arm nature of the trial prevents adequate interpretation of the results of time to event endpoint of OS which was a secondary endpoint of the trial. Given the severity and rarity of the disease condition with an associated high degree of morbidity and mortality, especially in metastatic disease, these outcomes represent a clinically meaningful benefit for patients. As with all other radiopharmaceuticals, iobenguane I 131 is associated with an increased risk for secondary hematologic malignancy including myelodysplastic syndrome or acute leukemias. Due to the risk of serious adverse reactions, iobenguane I 131 is only indicated for patients with unresectable, locally advanced or metastatic paraganglioma who require systemic anticancer therapy and have no other known curative options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2020</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>12/2019</td>
<td>BCBSA National medical policy review. Policy statement added that iobenguane I 131 is considered medically necessary when the specified conditions are met. Clarified coding information. Effective 12/1/2019.</td>
</tr>
<tr>
<td>1/2019</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>12/2018</td>
<td>New medical policy describing medically necessary and investigational indications. The use of Lutathera® (lutetium 177 dotate) is considered medically necessary for patients with gastroenteropancreatic, bronchopulmonary, and thymus neuroendocrine tumors. Effective 12/1/2018.</td>
</tr>
<tr>
<td></td>
<td>The use of Azedra® (iobenguane I-131) is considered investigational for patients aged 12 and older with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. Effective 12/1/2018.</td>
</tr>
</tbody>
</table>

### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References


