Clinical Policy Title: Gallium Ga68 dotatate

Clinical Policy Number: 09.01.14

Effective Date: March 1, 2017
Initial Review Date: February 15, 2017
Most Recent Review Date: February 6, 2018
Next Review Date: February 2019

Related policies:

CP# 18.01.03 Single photon emission computed tomography scans

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the use of gallium Ga68 dotatate (Netspot®) scans to be clinically proven and, therefore, medically necessary when the following criteria are met (Deppen, 2016; Nockel, 2016; Santhanam, 2015; Alonso, 2014; Tan, 2014; Haug, 2012; Catena, 2011; Schreiter, 2014; Sonmezoglu, 2016):

- Diagnosis, staging, restaging and monitoring are used to guide management of neuroendocrine tumors (NETs).

Limitations:

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at http://ahca.myflorida.com/Medicaid/.
All other uses of gallium Ga68 dotatate scans are not medically necessary and are considered investigational, including diagnosis, staging, restaging, and monitoring of multiple myeloma.

**Alternative covered services:**

Standard imaging modalities (e.g., computerized tomography [CT], magnetic resonance imaging [MRI], or ultrasound [US]).

**Background**

Gallium Ga 68 dotatate is an injectable radiopharmaceutical applicable to positron emission tomography (PET) imaging that is suitable for isolation of somatostatin receptor positive NETs. NETs are rare, sometimes malignant, tumors that develop in the hormone-producing cells of the stomach, intestines, pancreas (i.e., insulinoma), and lungs.

**Searches**

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 14, 2017. Search terms were: “gallium Ga68 dotatate.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

There is low- to moderate-quality medical evidence of safety and efficacy supportive of gallium Ga 68 dotatate PET scanning from several medium- to large-sized randomized controlled trials (RCTs) (Deppen, 2016; Nockel, 2016; Santhanam, 2015). These trials have favorably compared imaging of NETs with the
Ga 68 radiopharmaceutical to images obtained with other approved diagnostic radiography agents, and then confirmed with CT and/or MRI. Others (Alonso, 2014; Tan, 2014; Haug, 2012; Catena, 2011) evaluated Ga 68 dotatate images using histopathology and clinical follow-up as reference standards; and one RCT evaluated patients with NET recurrence using Ga 68 dotatate images (Schreiter, 2014). One small observational study (n = 21) (Sonmezoglu, 2016) opined that Ga 68 labelled dotatate scanning may play a complementary role in multiple myeloma diagnosis and management.

Policy updates:

During the past twelve months there has been no further information published regarding Gallium Ga68 dotatate.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deppen (2016)</td>
<td>Safety and efficacy of 68Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors</td>
</tr>
<tr>
<td></td>
<td>• An RCT inclusive of 97 adult patients (mean age 54; 41 men and 56 women) with known or suspected NETs who were evaluated with Ga 68 dotatate PET.</td>
</tr>
<tr>
<td></td>
<td>• Among 78 patients in whom CT and/or MRI images and In 111 pentetreotide images were available, Ga 68 dotatate PET was in agreement with the CT and/or MRI images of 74 patients.</td>
</tr>
<tr>
<td></td>
<td>• Out of 50 patients with NETs localized by CT and/or MRI imaging, Ga 68 dotatate was positive in 48 patients, including 13 patients in whom In 111 pentetreotide was negative.</td>
</tr>
<tr>
<td></td>
<td>• Ga 68 dotatate was negative in 26 out of 28 patients in whom CT and/or MRI imaging was negative.</td>
</tr>
<tr>
<td>Sadowski (2016)</td>
<td>Prospective study of 68Ga-dotatate positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites</td>
</tr>
<tr>
<td></td>
<td>• An RCT inclusive of 131 patients evaluated 68Ga dotatate PET/CT in detecting unknown primary and metastatic NETs.</td>
</tr>
<tr>
<td></td>
<td>• 68Ga dotatate PET/CT imaging detected 95.1% of lesions (95% CI, 92.4% to 96.8%) with an average maximum standardized uptake value of 65.4 6 47 (range, 6.9 to 244), while anatomic imaging detected 45.3% of lesions (95% CI, 37.9% to 52.9%).</td>
</tr>
<tr>
<td></td>
<td>• Over 30% of lesions (95% CI, 25.0% to 37.5%), were noted to have a significant difference between imaging modalities (P, .001).</td>
</tr>
<tr>
<td></td>
<td>• In four of 14 patients (28.6%), 68Ga dotatate PET/CT found a previously unknown primary tumor and detected primary NET, lymph node, and distant metastases correctly in 72 of 113 lesions (63.7%) when compared with histopathology.</td>
</tr>
<tr>
<td></td>
<td>• On the basis of findings with 68Ga dotatate PET/CT, 43 of 131 patients (32.8%) had a change in management recommendation.</td>
</tr>
<tr>
<td></td>
<td>• In patients with carcinoid symptoms but negative biochemical testing, 68Ga dotatate PET/CT detected lesions in 65.2% of patients.</td>
</tr>
<tr>
<td></td>
<td>• The authors concluded that 68Ga dotatate PET/CT imaging provides important information for accurate staging of NETs and selection of appropriate treatment.</td>
</tr>
<tr>
<td>Nockel (2016)</td>
<td>A retrospective analysis looked at 31 patients who were diagnosed using 68Ga-dotatate PET/CT scan and had an insulinoma confirmed on histology.</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------</td>
</tr>
</tbody>
</table>
| Localization of insulinoma using 68Ga-DOTATATE PET/CT scan | - The insulinomas were correctly localized in 17 out of 31 (55%) of patients by CT, in 17 out of 28 (61%) by MRI, in six out of 28 (21%) by US, and in nine out of 10 (90%) by 68Ga dotate.  
- In 19 out of 23 patients (83%), manual palpation identified insulinoma. In patients who had all four noninvasive imaging studies, CT was concordant with 68Ga dotate in six out of nine patients (67%); MRI in eight out of nine (78%); ultrasound in zero out of nine; and in one out of nine patients (11%) the lesion was only seen by 68Ga dotate.  
- The authors concluded that gallium 68Ga dotatate PET/CT identifies most insulinomas and may be considered as an adjunct imaging study when all imaging studies are negative and when a minimally invasive surgical approach is planned. |
| Sonmezoglu (2016) | **Key points:**  
- An observational study (n = 21) looked at the role of gallium-68-labelled dotatate PET/CT scanning in patients with multiple myeloma.  
- All patients had one or more PET-positive lesions.  
- There was a discordant result in four (19%) patients between scans.  
- Gallium-68-labelled dotatate scans showed 108 lesions in 19 patients.  
- No significant difference was found in terms of lesion numbers detected (P = 0.67).  
- However, the presence of diffuse bone marrow uptake of 68 labelled dotatate seems to be a predicting factor for overall survival (P = 0.033, hazard ratio: 15.2 and 95% confidence interval: 1.2 – 185.5).  
- The authors concluded that 68 labelled dotatate scanning seems to be an alternative imaging modality and may play a complementary role in multiple myeloma management, at least by providing a different pathobiological insight into the disease. |
| Nakamoto (2015) | **Key points:**  
- Retrospective study of 46 patients  
  - Fourteen patients underwent a PET/CT scan for detecting unknown primary tumors after histopathological confirmation of a NET at metastatic sites (group A).  
  - Seven patients underwent a PET/CT scan for detecting metastasis or recurrence after surgery for NET because of their high hormone levels but with no recurrence detected by other imaging modalities (group B).  
  - Twenty-five patients underwent a PET/CT scan for detecting suspected NETs because their hormone levels were high with no history of histopathologically proven NET (group C).  
- In group A, unknown primary tumors were suspected by PET/CT in eight of 14 patients (gastrointestinal/pancreatic NET in seven patients, prostatic cancer in one patient), but prostatic cancer was not confirmed by histopathology (i.e., false positive).  
- In group B, PET/CT depicted lesions in six of seven patients, including nodal metastasis (n = 5) and liver metastasis (n = 1).  
- In group C, PET/CT did not demonstrate any abnormal foci except in one case of pancreatic NET.  
- PET/CT was useful for detecting NETs, especially when recurrence or metastases were suspected because of high hormone levels after surgery for a NET. |
| Santhanam (2015) | **Key points:**  
- Narrative review considered that NETs with unknown primary tumor are associated with a poor prognosis (10-year survival 22%). |
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haug (2014)</strong>&lt;br&gt;Neuroendocrine tumor recurrence: diagnosis with 68Ga-DOTATATE PET/CT</td>
<td>• There is evidence that an effort should be made to localize the primary tumor even in the presence of metastasis because resection of the primary tumor or tumors may improve disease-free and overall survival.&lt;br&gt;• Localization of the tumors remains challenging and often relies on a combination of radiological, endoscopic, and functional imaging.&lt;br&gt;• Newer PET radiotracers such as 68 labelled dotatate somatostatin analogs such as gallium-68 dotatate have shown promise.&lt;br&gt;• In the near future, it is expected that patients with NET will benefit from newly developed PET approaches (radiopharmaceuticals) and intraoperative PET imaging.</td>
</tr>
<tr>
<td><strong>Schreiter (2014)</strong>&lt;br&gt;Searching for primaries in patients with neuroendocrine tumors (NET) of unknown primary and clinically suspected NET: Evaluation of Ga-68 DOTATOC PET/CT and In-111 DTPA octreotide SPECT/CT</td>
<td><strong>Key points:</strong>&lt;br&gt;• An RCT (n = 123) evaluated the clinical efficacy of In-111 octreotide CT and Ga-68 gallium-68 PET/CT for detection of primary tumors in patients with either neuroendocrine tumor of unknown primary or clinically suspected primary NET.&lt;br&gt;• The standard of reference included histopathology or clinical verification based on follow-up examinations.&lt;br&gt;• Ga-68 gallium-68 detected primaries in 15 patients (45.5%) and In-111 octreotide in four patients (8%) (p &lt; 0.001); in the suspected primary NET group, only two primaries could be detected, all by Ga-68 dotatate.&lt;br&gt;• Primary tumors could be found significantly more often than in patients with suspected NET (p = 0.01).&lt;br&gt;• Out of these 21 patients, 14 patients were operated.&lt;br&gt;• The authors concluded that Ga-68 dotatate PET/CT is preferable to In-111 octreotide when searching for primary NETs.</td>
</tr>
<tr>
<td><strong>Tan (2014)</strong>&lt;br&gt;Diagnostic value of 68Ga-DOTATATE PET/CT in liver metastases of neuroendocrine tumours of unknown origin</td>
<td><strong>Key points:</strong>&lt;br&gt;• An RCT of six patients (male:female = 5:1, age range 28 – 56 years) evaluated the diagnostic value of 68Ga dotatate PET/CT as part of a multimodality approach in neuroendocrine liver metastases of unknown primary.&lt;br&gt;• Clinical findings, histopathology, comparative imaging and follow-up were used to validate the results when ethically justified.&lt;br&gt;• Gallium 68Ga dotatate PET/CT identified the primary tumor in five out of six (83.3 %) patients: pancreas (n = 4) and stomach (n = 1).&lt;br&gt;• Out of three patients with indeterminate primary on initial CT, two patients were confirmed by 68Ga dotatate PET/CT.&lt;br&gt;• Absence of uptake in indeterminate primary of one patient was later confirmed negative by histopathology.&lt;br&gt;• In another three patients with undetected primary on initial CT, primary site was demonstrated in all patients with unsuspected metastases in two patients on 68Ga-dotatate PET/CT.</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------</td>
</tr>
</tbody>
</table>
| Alonso (2014) | - No further work-up was done to confirm the primary in patients with distant metastases.  
- Change of management was observed in three out of six (50%) patients.  
 Gallium (68)Ga-DOTATATE PET/CT in the evaluation of patients with neuroendocrine metastatic carcinoma of unknown origin |
| Key points: | - Retrospective study of twenty-nine patients (mean age 59.5 +/- 10.6 years; female 17) with pathologically proven neuroendocrine metastases.  
- In all cases, conventional imaging was negative for primary tumor identification.  
- Gallium (68)Ga dotatate PET/CT was performed with a mean dose of 104.2 +/- 18.8 MBq, using a 64-slice PET/CT with time-of-flight correction.  
- Gallium (68)Ga dotatate PET/CT identified the primary tumor in 17/29 (59%) patients in the following locations: pancreas (n = 7), ileum (n = 7), duodenum (n = 1), colon (n = 1), and stomach (n = 1).  
- Additional sites of unsuspected metastases were demonstrated in nine patients of this group and in six patients in whom no primary tumor was localized, mainly in lymph nodes and mesentery. |
| Sharma (2014) | PET/CT imaging of neuroendocrine tumors with (68)Gallium-labeled somatostatin analogues: An overview and single institutional experience from India |
| Key points: | - Narrative review cited NETs as rare neoplasms characterized by overexpression of somatostatin receptors (SSTRs).  
- Functional imaging plays a crucial role in management of NETs.  
- Authors concluded that PET-CT with gallium ((68)Ga)-labeled somatostatin analogues offers excellent results for imaging of NETs. |
| Naswa (2012) | 68Ga-DOTANOC PET/CT in patients with carcinoma of unknown primary of neuroendocrine origin |
| Key points: | - An RCT (n = 20) evaluated the role of Ga dotatate (Gallium-labeled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-Nal-octreotide) PET/CT for localization of the primary tumor in patients with carcinoma of unknown primary of neuroendocrine origin.  
- PET/CT was done after injection of 132 – 222 (4-6 mCi) of Ga dotatate. Images were evaluated by two experienced nuclear medicine physicians, both qualitatively as well as quantitatively (maximum standardized uptake value).  
- Ga dotatate PET/CT localized the primary tumor in 12/20 (60%) patients:  
  - Midgut was the most common site of primary tumor (n = 9); duodenum (four), ileum (four), and colon (one).  
  - In one patient each the primary was localized to the pancreas, stomach, and lung.  
  - In 12 patients, significant correlation was found between maximum standardized uptake value of primary tumor and metastasis (rho = 0.615; P = 0.041).  
- Even in patients in whom no primary tumor was localized, additional sites of metastatic disease were observed when compared with conventional imaging, mostly in lymph nodes and bones.  
- There was a change in management in three of 20 patients (15%), who underwent surgery. In the remaining 17 patients, demonstration of somatostatin receptor expression by PET/CT made them suitable candidates for peptide receptor radionuclide therapy. |
| Haug (2012) | |
The role of 68Ga-DOTATATE PET/CT in suspected neuroendocrine tumors

- An RCT (n = 104) studied patients (mean age 58; 52 men and 52 women) with suspected NETs due to clinical symptoms, elevated levels of tumor markers, or indeterminate tumors suggestive of NET.
- Diagnostic performance of Ga 68 dotatate PET in localizing tumor sites was retrospectively assessed using a reference standard: histopathology (n = 49) or clinical follow-up of up to five-month duration (n = 55).
- Images were interpreted by consensus between two on-site readers who were not blinded to clinical information.
- NET sites were localized by reference standard in 36 patients (all by histopathology).
- Out of these, Ga 68 dotatate was positive, correctly identifying a NET site, in 29 patients, and was falsely negative in seven.
- In 68 patients with no NET identified by a reference standard, the images were negative in 61 and falsely positive in seven patients.

Key points:

- A large RCT studied 750 neuroendocrine tumor patients, 82 of whom (10.9%) were diagnosed as having neuroendocrine tumors of an unknown primary site.
- The 82 patients with neuroendocrine tumors of an unknown primary site (34 males) had a median age of 60 years; 57 (69.5%) had histologically well-differentiated tumors, three (3.7%) had poorly differentiated tumors, and 22 (26.8%) had tumors that could not be classified.
- Thirty-one patients (37.8%) underwent metastatic site surgery, which was radical in 11 cases (35.4%).
- Forty-eight patients (58.5%) received somatostatin analogues, and 41 (50.0%) underwent chemotherapy.
- At the end of the study period, 59 patients (72.0%) had died, 31 (53.0%) because of disease progression, and 23 (28.0%) were still alive.

References

Professional society guidelines/other:


Peer-reviewed references:


Deppen S, Liu E, Blume J. Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and


CMS National Coverage Determinations (NCDs):


Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3A.8</td>
<td>Neuroendocrine tumor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A9587</td>
<td>Gallium GA-68, dotatate, diagnostic, 0.1 millicurie</td>
<td></td>
</tr>
</tbody>
</table>