Clinical Policy: Ipilimumab (Yervoy)
Reference Number: CP.PHAR.319
Effective Date: 04.17.18
Last Review Date: 02.21
Line of Business: Commercial, HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description Ipilimumab (Yervoy®) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody.

FDA Approved Indication(s)
Yervoy is indicated for:

• **Melanoma**
  o Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older)
  o Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy

• **Renal cell carcinoma (RCC)**
  o Treatment of patients with intermediate or poor risk, previously untreated advanced RCC, in combination with nivolumab

• **Colorectal Cancer (CRC)**
  o Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab*

• **Hepatocellular carcinoma (HCC)**
  o In combination with nivolumab, the treatment of patients with HCC who have been previously treated with sorafenib*

• **Non-small cell lung cancer (NSCLC)**
  o In combination with nivolumab, for the first-line treatment of adult patients with metastatic NSCLC whose tumors express programmed death-ligand 1 (PD-L1) ≥ 1% as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations
  o In combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations

• **Malignant pleural mesothelioma**
  o Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.

*This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Yervoy is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Melanoma (must meet all):
      1. Diagnosis of unresectable, metastatic or lymph node positive melanoma;
      2. Prescribed by or in consultation with an oncologist;
      3. Age ≥ 12 years;
      4. Request meets one of the following (a or b):*
         a. Unresectable or metastatic disease: Dose does not exceed 10 mg per kg;
         b. Adjuvant treatment: Dose does not exceed 3 mg/kg per dose for a maximum of 4 doses over 16 weeks;
         c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN

   Approval duration: 6 months

   B. Renal Cell Carcinoma (must meet all):
      1. Diagnosis of RCC;
      2. Prescribed by or in consultation with an oncologist;
      3. Age ≥ 12 years;
      4. Prescribed in combination with Opdivo®,*
         *Prior authorization may be required for Opdivo
      5. Request meets one of the following (a or b):*
         a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
         b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN

   Approval duration: 16 weeks (maximum of 4 doses)

   C. Colorectal Cancer (must meet all):
      1. Diagnosis of MSI-H or dMMR CRC;
      2. Prescribed by or in consultation with an oncologist;
      3. Age ≥ 12 years;
      4. Disease is unresectable or metastatic;
      5. Prescribed in combination with Opdivo;
      6. Request meets one of the following (a or b):*
         a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
         b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   *Prescribed regimen must be FDA-approved or recommended by NCCN

   Approval duration: 16 weeks (maximum of 4 doses)
D. **Hepatocellular Carcinoma** (must meet all):
   1. Diagnosis of HCC;
   2. Prescribed by or in consultation with an oncologist;
   3. Age ≥ 18 years;
   4. Member has previously received Nexavar® or Lenvima®;
      *Prior authorization may be required for Nexavar and Lenvima*
   5. Prescribed in combination with Opdivo;
      *Prior authorization may be required for Opdivo*
   6. Documentation of Child-Pugh Class A status;
   7. Member has not had previous treatment with a checkpoint inhibitor (e.g., Opdivo, Keytruda®, Tecentriq®, Imfinzi®);
   8. Request meets one of the following (a or b):*
      a. Dose does not exceed 3 mg/kg IV every 3 weeks for a maximum of 4 doses;
      b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
      *Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:** 16 weeks (maximum of 4 doses)

E. **Non-Small Cell Lung Cancer** (must meet all):
   1. Diagnosis of recurrent, advanced or metastatic NSCLC;
   2. Prescribed by or in consultation with an oncologist;
   3. Age ≥ 18 years;
   4. Prescribed in combination with Opdivo;
      *Prior authorization may be required for Opdivo*
   5. Member has not previously progressed on a PD-1/PD-L1 inhibitor (e.g., Opdivo, Keytruda, Tecentriq, Imfinzi);
   6. Request meets one of the following (a, b, c, or d):*
      a. For use in combination with Opdivo for tumors positive for the Tumor Mutation Burden (TMB) biomarker;
      b. Disease mutation status is unknown or negative for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET, and member has not received prior systemic therapy for advanced disease;
      c. Disease mutation status is positive for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, RET, or NTRK gene fusion, and member has received mutation-specific treatment;
      d. Disease is positive for a RET rearrangement;
      *Prior authorization may be required for Opdivo*
   7. Request meets one of the following (a or b):
      a. Member has PD-L1 tumor expression of ≥ 1%;
      b. Yervoy is being used in combination with Opdivo ± a platinum-based regimen (see Appendix B);
   8. Request meets one of the following (a or b):*
      a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
      b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
      *Prescribed regimen must be FDA-approved or recommended by NCCN*
Approval duration: 6 months

F. Malignant Pleural Mesothelioma (must meet all):
   1. Diagnosis of unresectable malignant pleural mesothelioma;
   2. Prescribed by or in consultation with an oncologist;
   3. Age ≥ 18 years;
   4. Prescribed in combination with Opdivo;*
      *Prior authorization may be required for Opdivo.
   5. Request meets one of the following (a or b):*
      a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
      b. Dose is supported by practice guidelines or peer-reviewed literature for the
         relevant off-label use (prescriber must submit supporting evidence).
      *Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 6 months

G. NCCN Compendium Indications (off-label) (must meet all):
   1. Diagnosis of one of the following (a, b, or c):
      a. Small cell lung cancer (SCLC);
      b. MSI-H or dMMR small bowel adenocarcinoma;
      c. Uveal melanoma;
   2. Prescribed by or in consultation with an oncologist;
   3. Age ≥ 12 years;
   4. For SCLC or MSI-H/dMMR small bowel adenocarcinoma: Prescribed in combination
      with Opdivo;*
      *Prior authorization may be required for Opdivo.
   5. For uveal melanoma: Prescribed as a single agent or in combination with Opdivo;*
      *Prescribed regimen must be FDA-approved or recommended by NCCN
   6. For SCLC: Failure of a platinum-containing regimen (e.g. cisplatin, carboplatin),
      unless clinically significant adverse effects are experienced or all are contraindicated;
   7. Dose is within FDA maximum limit for any FDA-approved indication or is supported
      by practice guidelines or peer-reviewed literature for the relevant off-label use
      (prescriber must submit supporting evidence).*
      *Prescribed regimen must be FDA-approved or recommended by NCCN

Approval duration: 6 months

H. Other diagnoses/indications
   1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT
      specifically listed under section III (Diagnoses/Indications for which coverage is
      NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance
      marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy
A. Melanoma - Unresectable or Metastatic
   1. Reauthorization beyond 16 weeks is not permitted. Members must meet the initial
      approval criteria, at a minimum of 3 months since initial treatment discontinuation.

Approval duration: Not applicable

B. Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma
1. Reauthorization beyond 16 weeks is not permitted. Members must meet the initial approval criteria.

**Approval duration:** Not applicable

C. Melanoma (Adjuvant Treatment), Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma (must meet all):
   1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Yervoy and has received this medication for at least 30 days;
   2. Member is responding positively to therapy;
   3. If request is for a dose increase, request meets one of the following (a, b, or c):*
      a. For melanoma: New dose does not exceed 10 mg/kg per dose;
      b. For NSCLC and malignant pleural mesothelioma: New dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
      c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence).*

   *Prescribed regimen must be FDA-approved or recommended by NCCN
   
   **Approval duration:** 12 months or up to a total duration of 3 years (cutaneous melanoma) or 2 years (NSCLC, malignant pleural mesothelioma), whichever is less

D. NCCN Compendium Indications (off-label) (must meet all):
   1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Yervoy for a covered indication and has received this medication for at least 30 days;
   2. Member is responding positively to therapy;
   3. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence).*

   *Prescribed regimen must be FDA-approved or recommended by NCCN
   
   **Approval duration:** 12 months

E. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

   **Approval duration:** Duration of request or 6 months (whichever is less); or
   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information
Appendix A: Abbreviation/Acronym Key

- ALK: anaplastic lymphoma kinase
- BRAF: B-Raf proto-oncogene, serine/threonine kinase
- CRC: colorectal cancer
- CTLA-4: cytotoxic T-lymphocyte antigen 4
- dMMR: mismatch repair deficient
- EGFR: epidermal growth factor receptor
- FDA: Food and Drug Administration
- HCC: hepatocellular carcinoma
- MET: mesenchymal-epithelial transition
- MSI-H: microsatellite instability-high
- PD-1: programmed death-1
- PD-L1: programmed death-ligand 1
- RCC: renal cell carcinoma
- ROS1: ROS proto-oncogene 1
- SCLC: small cell lung cancer
- TMB: Tumor Mutation Burden
- TLS: T-cell lymphoma/lymphoblastic
- TSS: T-cell small cell sarcoma
- VEGF: vascular endothelial growth factor
- VHL: von Hippel-Lindau disease
- V600E: V600E is the common activating mutation in B-Raf

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opdivo (nivolumab)</td>
<td></td>
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<tr>
<td></td>
<td>SCLC</td>
<td>1 mg/kg to 3 mg/kg IV every 2 weeks with or without ipilimumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>MSI-H/dMMR Small bowel adenocarcinoma</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg/kg IV once every 3 weeks for four doses, then 3 mg/kg IV or 240 mg IV every 2 weeks with or without ipilimumab</td>
</tr>
<tr>
<td>cisplatin- or carboplatin-containing regimen</td>
<td>SCLC</td>
<td>Varies</td>
</tr>
<tr>
<td>Nexavar (sorafenib)</td>
<td>HCC</td>
<td>400 mg PO BID</td>
</tr>
<tr>
<td>Lenvima (lenvatinib)</td>
<td>HCC</td>
<td>12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients &lt; 60 kg)</td>
</tr>
<tr>
<td>platinum-containing regimens</td>
<td>NSCLC – squamous cell carcinoma</td>
<td>paclitaxel + carboplatin dose varies</td>
</tr>
<tr>
<td></td>
<td>NSCLC – nonsquamous cell carcinoma</td>
<td>pemetrexed + [carboplatin or cisplatin] dose varies</td>
</tr>
</tbody>
</table>

Therapeutic alternatives are listed as **Brand name®** (generic) when the drug is available by brand name only and **generic (Brand name®)** when the drug is available by both brand and generic.

Appendix C: Contraindications and Boxed Warnings
- Bristol-Myers Squibb was released from the REMS program for Yervoy in March 2015.
- Boxed warning(s): immune-mediated adverse reactions
- Contraindication(s): none reported

**Appendix D: General Information**
- NCCN lists Yervoy in combination with Opdivo with a category 2A recommendation for use in small cell lung cancer as subsequent systemic therapy for patients with:
  - Performance status 0-2 with relapse within 6 months following complete or partial response
  - Stable disease with initial treatment
  - Patients with primary progressive disease.

### V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma (adjuvant treatment)</td>
<td>10 mg/kg IV every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity.</td>
<td>10 mg/kg/dose</td>
</tr>
<tr>
<td>Melanoma (unresectable or metastatic)</td>
<td>3 mg/kg IV every 3 weeks for a total of 4 doses</td>
<td>3 mg/kg/dose</td>
</tr>
<tr>
<td>RCC</td>
<td>Nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
<td>1 mg/kg/dose</td>
</tr>
<tr>
<td>CRC</td>
<td>Nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses or until intolerable toxicity or disease progression, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
<td>1 mg/kg/dose</td>
</tr>
<tr>
<td>HCC</td>
<td>Nivolumab 1 mg/kg IV, followed by ipilimumab 3 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</td>
<td>3 mg/kg/dose</td>
</tr>
</tbody>
</table>
| NSCLC                                | In combination with nivolumab: nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression
  
  In combination with nivolumab and platinum-doublet chemotherapy: nivolumab 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease | 1 mg/kg/dose    |
CLINICAL POLICY
Ipilimumab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>progression, unacceptable toxicity, or up to 2 years in patients without disease progression</td>
<td></td>
</tr>
<tr>
<td>Malignant pleural mesothelioma</td>
<td>1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.</td>
<td>1 mg/kg/dose</td>
</tr>
</tbody>
</table>

VI. Product Availability
Single-use vials: 50 mg/10 mL, 200 mg/40 mL

VII. References

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>J9228</td>
<td>Injection, ipilimumab, 1 mg</td>
</tr>
</tbody>
</table>

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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</thead>
<tbody>
<tr>
<td>01.17</td>
<td>03.17</td>
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Policy split from CP.PHAR.182 Excellus Oncology. Off-label NCCN recommended uses added.
<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added age limit of $\geq 12$ years per package labeling. Added coverage criteria for small cell lung cancer. Previously the off-label diagnosis was covered, but without any coverage requirements. Added off-label NCCN recommended uses for malignant pleural mesothelioma and brain metastases from melanoma. For Continued Therapy, removed requirement to check for safety-related reasons to discontinue therapy, per the PA Policy for Safety Precautions.</td>
<td>08.29.17</td>
<td>11.17</td>
</tr>
<tr>
<td>Criteria added for new FDA indication: advanced renal cell carcinoma in combination with nivolumab; removed malignant pleural mesothelioma due to NCCN 2B recommendation status; added oncologist specialist requirement for all covered indications; summarized NCCN and FDA-approved uses for improved clarity; added up to a total tx duration of 3 years for cutaneous melanoma per PI; added failure of platinum-containing chemotx for SCLC per NCCN; allowed continuity of care for continued approval; clarified continued therapy language for unresectable or metastatic melanoma that reauthorization beyond 16 weeks is not permitted from reauthorization is not permitted; references reviewed and updated. Criteria added for new FDA indication: colorectal cancer in combination with nivolumab; references reviewed and updated.</td>
<td>07.24.18</td>
<td>08.18</td>
</tr>
<tr>
<td>2Q 2019 annual review: added coverage for malignant pleural mesothelioma; references reviewed and updated.</td>
<td>02.05.19</td>
<td>05.19</td>
</tr>
<tr>
<td>2Q 2020 annual review: added commercial line of business and revised HIM-medical benefit to HIM line of business; added NCCN compendium-supported indications of small bowel adenocarcinoma and uveal melanoma; condensed NCCN compendium-supported indications into one subsection; references reviewed and updated.</td>
<td>02.16.20</td>
<td>05.20</td>
</tr>
<tr>
<td>Added FDA-labeled indications of HCC and NSCLC in combination with Opdivo; references reviewed and updated.</td>
<td>06.23.20</td>
<td>08.20</td>
</tr>
<tr>
<td>RT4: FDA approved malignant pleural mesothelioma added. Ad hoc changes: melanoma unresectable/metastatic disease and lymph node positive disease criteria sets combined; for HCC, Lenvima added as a prior therapy option per NCCN; for NSCLC, single agent therapy for TMB positive tumor added and combination therapy for RET rearrangement added per NCCN, combination therapy changed from Yervoy and platinum doublet therapy to Yervoy plus/minus a platinum based regimen to accommodate NCCN recommended uses; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.</td>
<td>11.18.20</td>
<td>02.21</td>
</tr>
</tbody>
</table>

**Important Reminder**
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.