I. PURPOSE

To define and describe the accepted indications for Yervoy (ipilimumab) usage in the treatment of cancer.

II. DEFINITIONS

Yervoy (ipilimumab): is a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands CD80/CD86. CTLA-4 is a negative regulator of T-cell activation. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab’s effect in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses.

Yervoy (ipilimumab) is FDA approved for the treatment of patients with unresectable or metastatic melanoma and for the 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.

Yervoy (ipilimumab) is available in solution for injection; 50 mg and 200 mg.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must be supported by, at minimum, two peer reviewed citations. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Yervoy (ipilimumab) may be considered medically necessary when any of the following selection criteria is met:

1. Melanoma
   a. Yervoy (ipilimumab) is being used for any of the following:
      i. Unresectable or metastatic diseaseas ONE of the following:
         1. First line therapy in combination with Opdivo (nivolumab) if clinical stability is anticipated for >12 weeks and ECOG is 0-1
2. Second-line or subsequent therapy as a single agent or in combination with Opdivo (nivolumab) for disease progression and performance status 0-2

3. Reinduction in select members who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease greater than three months.

ii. Adjuvant treatment as a high-dose single agent for stage IIIA with metastases >1 mm or stage IIIB-C disease with nodal metastases following a complete lymph node dissection or nodal recurrence.

**Exclusion Criteria:** Yervoy (ipilimumab) is not considered medically necessary when any of the following selection criteria is met:

1. Members who experience severe or life-threatening reactions to Yervoy (ipilimumab) including any moderate immune mediated adverse events or symptomatic endocrinopathy.
2. Disease progression while taking Yervoy (ipilimumab).
3. Dosing exceeds single dose limit of Yervoy (ipilimumab) 10 mg/kg.
4. Treatment for unresectable or metastatic disease exceeds the maximum duration limit, from the administration of the initial dose, of 16 weeks or 4 total doses.
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

**IV. PROCEDURE**

Requests for Yervoy (ipilimumab) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration:**
   a. Unresectable or Metastatic Melanoma: 3 mg/kg IV infusion over 90 minutes every 3 weeks for a total of 4 doses; permanently discontinue if treatment cannot be completed within 16 weeks.
   
   b. Adjuvant Treatment of Melanoma: 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses followed by 10 mg/kg every 12 weeks for up to 3 years.

2. **Dosage Adjustments**
   a. Moderate immune-mediated adverse reactions or for symptomatic endocrinopathy: withhold scheduled dose; in patients with partial or complete resolution of adverse reactions (Grade 0 to 1) AND who are receiving less than 7.5 mg of prednisone or equivalent per day, may restart at 3 mg/kg IV every 3 weeks until administration of all 4 planned doses or 16 weeks from the first dose, whichever comes first.
   
   b. Persistent moderate adverse reactions or inability to decrease corticosteroid dose to 7.5 mg prednisone or equivalent per day: permanently discontinue ipilimumab.
c. If full treatment course cannot be completed within 16 weeks: permanently discontinue ipilimumab.

d. Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more from baseline), stool incontinence, need for IV hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation: permanently discontinue ipilimumab.

e. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than 5 times the ULN or total bilirubin level greater than 3 times the ULN: permanently discontinue ipilimumab.

f. Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations: permanently discontinue ipilimumab.

g. Severe motor or sensory neuropathy, Guillain-Barre syndrome, or myasthenia gravis: permanently discontinue ipilimumab.

h. Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, noninfectious myocarditis: permanently discontinue ipilimumab.

i. Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy: permanently discontinue ipilimumab.

3. Monitoring
   a. Objective evidence of tumor regression is indicative of efficacy.
   j. Clinical chemistries at baseline and before each dose.
   k. Liver function tests at baseline and before each dose.
   l. Thyroid function tests at baseline and before each dose.
   m. Signs of immune-mediated enterocolitis (eg, blood or mucus in the stool).
   n. Signs of bowel perforation such as ileus.
   o. Signs of immune-mediated endocrinopathies such as hypophysitis; imaging studies may be considered.

V. APPROVAL AUTHORITY
   1. Review – UM Department
   2. Final Approval – UM Committee

VI. ATTACHMENTS

VII. REFERENCES