Market Applicability							
Market	**DC**	**GA**	**KY**	**MD**	**NJ**	**NY**	**WA**
Applicable	X	X	X	X	X	X	X

Yervoy (ipilimumab)

Override(s)	Approval Duration
Prior Authorization	1 year

Medications
Yervoy (ipilimumab)

APPROVAL CRITERIA

Requests for Yervoy (ipilimumab) may be approved the following criteria are met:

I. Individual is using for the treatment of Colorectal Cancer; **AND**
   A. Individual meets one of the following criteria:
      1. Primary treatment used in combination with nivolumab for unresectable metachronous metastases (defective mismatch repair/high microsatellite instability [dMMR/MSIH] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; **OR**
      2. Yervoy (ipilimumab) is used in combination with nivolumab as subsequent therapy for unresectable advanced or metastatic colorectal cancer with defective mismatch repair (dMMR) or high microsatellite instability (MSIH) mutations that has progressed following treatment with fluoropyrimidine and oxaliplatinor irinotecan;

   AND
   B. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
   C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

II. Individual has a diagnosis of advanced Hepatocellular Carcinoma and the following criteria are met:
   A. Individual is using in combination with nivolumab (Opdivo); **AND**
   B. Confirmation of disease progression on or had intolerance to sorafenib; **AND**
   C. Individual has a current ECOG performance status of 0-2; **AND**
   D. Individual has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**

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Applicable	X	X	X	X	X	X	X

E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

III. Individual has a diagnosis of metastatic Melanoma with brain metastases (NCCN 2A); **AND**
   A. Individual has a primary diagnosis of melanoma; **AND**
   B. Individual has asymptomatic brain metastases (Long 2017, 2018, Tawbi 2017); **AND**
   C. Individual is using in combination with nivolumab; **AND**
   D. Individual has not received treatment with another anti-PD-1, anti-PD-L1 agent, or anti-CTLA-4 agent; **AND**
   E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IV. Individual is using for the treatment of unresectable or metastatic Melanoma (Cutaneous and Uveal); **AND**
   A. An individual has an ECOG performance status of 0-2; **AND**
   B. Yervoy (ipilimumab) is used in combination with nivolumab (Opdivo) as:
      1. First-line therapy (NCCN 1); **OR**
      2. Second-line or subsequent therapy for disease progression if Opdivo (nivolumab) was not previously used (NCCN 2A); **OR**
   C. Yervoy (ipilimumab) is used as a single agent for one of the following:
      1. First line therapy as a single course of 4 treatments; **OR**
      2. Second-line or subsequent lines of therapy as a single course of 4 treatments (NCCN 2A); **OR**
      3. Retreatment, consisting of a 4-dose limit, for an individual who had no significant systemic toxicity during prior Yervoy therapy and whose disease progressed after being stable for greater than 3 months following completion of a prior course of Yervoy, and for whom no intervening therapy has been administered (NCCN 2A);

OR

V. Individual is using for the adjuvant treatment of Melanoma (Cutaneous and Uveal) in individual with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including lymphadenectomy.

OR

VI. Individual is using for the first-line treatment of stage IV or recurrent non-small cell lung cancer (NSCLC) (NCCN 2A); **AND**

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Applicable	X	X	X	X	X	X	X

A. Yervoy (ipilimumab) is used in combination with nivolumab (Opdivo); **AND**
B. Cytologically confirmed stage IV or recurrent NSCLC; **AND**
C. High tumor mutation burden (greater than or equal to 10 mutations per megabase); **AND**
D. No sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations in nonsquamous carcinoma; **AND**
E. Has not received prior systemic therapy as primary therapy for advanced or metastatic NSCLC; prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior; **AND**
F. Individual has an ECOG performance status of 0-2; **AND**
G. Individual is not receiving therapy for an autoimmune disease, chronic condition or interstitial lung disease with a systemic immunosuppressant;

OR

VII. Individual is using for first line treatment of recurrent, advanced, or metastatic Non-Small Cell Lung Cancer (NSCLC) (Label, NCCN 2A); **AND**
A. Individual is using in combination with nivolumab; **AND**
B. Individual does not have presence of EGFR, ALK, ROS1, or BRAF mutations;

AND
C. Current ECOG performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. Individual is using for first line treatment of recurrent or metastatic Non-Small Cell Lung Cancer (NSCLC); **AND**
A. Individual is using in combination with nivolumab *and* 2 (two) cycles of platinum-doublet chemotherapy (i.e., platinum-based chemotherapy with pemetrexed, or carboplatin with paclitaxel); **AND**
B. Individual does not have presence of EGFR, ALK, ROS1, or BRAF mutations; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. Has not received treatment with another anti-PD-1 or anti-PD-L1 agent; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

VIII. Individual is using for the treatment intermediate- or poor-risk, advanced Renal Cell Carcinoma (RCC); **AND**
A. Yervoy (ipilimumab) is used in combination with nivolumab (Opdivo) for four cycles

Market Applicability							
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Applicable	X	X	X	X	X	X	X

followed by single agent nivolumab (Opdivo), as first-line therapy for previously untreated RCC; **OR**

B. Yervoy (ipilimumab) is used in subsequent therapy with nivolumab (Opdivo) for four cycles followed by single agent nivolumab (Opdivo),if no checkpoint blockade (PD-1, PD-L1, or CTLA-4) antibody treatment has been previously administered (NCCN 2A);

AND

C. Histologic confirmation of RCC with clear-cell component; **AND**
D. Individual has an ECOG performance status 0-2; **AND**
E. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

IX. Individual has a diagnosis of Small Bowel Adenocarcinoma (SBA) (NCCN 2A); **AND**
A. Individual has advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only); **AND**
B. Individual is using in combination with nivolumab as subsequent therapy; **AND**
C. Current ECOG performance status of 0-2; **AND**
D. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant;

OR

X. Individual is using for the treatment of Small Cell Lung Cancer (NCCN 2A); **AND**
A. Individual has an ECOG performance status of 0-2; **AND**
B. Yervoy is used in combination with nivolumab (Opdivo) as subsequent therapy for one of the following (NCCN 2A):
1. Demonstrated disease relapse within 6 months following complete or partial response or stable with initial treatment; **OR**
2. No response with initial treatment; **OR**
3. Primary progressive disease;

OR

XI. Individual is using for the treatment of malignant pleural mesothelioma (NCCN 2A); **AND**
A. Individual is using in combination with nivolumab (Opdivo) for subsequent therapy; **AND**
B. Individual has an ECOG performance status of 0-2; **AND**
C. Individual is not receiving therapy for an autoimmune disease or chronic condition requiring treatment with a systemic immunosuppressant.

Requests of Yervoy (ipilimumab) may not be approved for the following:

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Market	**DC**	**GA**	**KY**	**MD**	**NJ**	**NY**	**WA**
Applicable	X	X	X	X	X	X	X

I. Individual has an autoimmune disease which requires treatment with immunosuppressant drugs; **OR**
II. When the above criteria are not met and for all other indications.

Note:
Yervoy has a black box warning for severe and fatal immune-mediated adverse reactions. The most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis, neuropathy, and endocrinopathy, but the reactions can involve any organ system. The majority of the immune-mediated reactions manifested during treatment; however, a minority occurred weeks to months after discontinuation. Assess individuals for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy, and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. Permanently discontinue Yervoy and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

Key References:

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: May 28, 2020.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018; 378(22):2093-2104.
4. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Eng J Med.* 2019;381:2020-31.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2019; Updated periodically.
6. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicenter randomized phase 2 study. *Lancet Oncol.* 2018;19:672-81.
7. Long GV, Atkinson V, Menzies AM, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients with melanoma brain metastases: the Anti-PD1 Brain Collaboration. *J Clin Oncol.* 2017;35:9508[abstract]. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9508.
8. NCCN Clinical Practice Guidelines in Oncology™. © 2020 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on May 28, 2020.
    a. Central Nervous System Cancers. V3.2019. Revised October 18, 2019.
    b. Colon Cancer. V1.2020. Revised December 19, 2019.
    c. Kidney Cancer. V2.2020. Revised August 5, 2019.
    d. Malignant Pleural Mesothelioma. V1.2020. Revised November 27, 2019.
    e. Cutaneous Melanoma. V1.2020. Revised December 19, 2019.
    f. Non-Small Cell Lung Cancer. V5.2020. Revised May 27, 2020.
    g. Rectal Cancer. V1.2020. Revised December 19, 2019.
    h. Small Bowel Adenocarcinoma V1.2020. Revised July 30, 2019.
    i. Small Cell Lung Cancer. V2.2020. Revised November 15, 2019.
    j. Uveal Melanoma. V1.2019. Revised June 14, 2019.

This policy does not apply to health plans or member categories that do not have pharmacy benefits, nor does it apply to Medicare. Note that market specific restrictions or transition-of-care benefit limitations may apply.

Market Applicability							
Market	**DC**	**GA**	**KY**	**MD**	**NJ**	**NY**	**WA**
Applicable	X	X	X	X	X	X	X

9. Margolin K, Ernstoff MS, Hamid O. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012; 13(5):459-465.
10. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol.* 2018;36:773-9. Available at: https://ascopubs.org/doi/pdf/10.1200/JCO.2017.76.9901.
11. Tawbi HA, Forsyth AJ, Algazi AP, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: results of the phase II study CheckMate 204. *J Clin Oncol.* 2017;35:9507-9507[abstract]. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9507.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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