Effective November 1, 2018, refer to Palmetto Article A56141

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Yervoy (ipilimumab)

Policy #:	667	Effective Date:	November 6, 2016
Category:	Pharmacology	Latest Review Date:	October 2017

Background:
Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Yervoy® (ipilimumab) is a human monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). It blocks the interaction of CTLA-4 with its ligands of CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. CTLA-4 acts as a "switch" to inactivate these T cells, thereby reducing the strength of immune responses; ipilimumab binds to CTLA-4 and prevents it from sending its inhibitory signal. Yervoy may work by allowing the body's immune system to recognize, target and attack cells in melanoma tumors.

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service on or after November 6, 2016 and prior to November 1, 2018:

Blue Advantage will treat **Yervoy® (ipilimumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** and the individual does not have an active autoimmune disease.

Blue Advantage will treat **Yervoy® (ipilimumab)** as a **covered benefit** for the **retreatment of unresectable or metastatic melanoma** as a **single agent** when the individual does not have an active autoimmune disease and ***all*** of the following are met:

- experienced no significant systemic toxicity during prior medically necessary Yervoy (ipilimumab) therapy; **and**
- relapsed after initial clinical response or progressed after stable disease greater than 3 months following completion of prior Yervoy (ipilimumab) therapy

Blue Advantage will treat **Yervoy® (ipilimumab)** as a **covered benefit** for adjuvant treatment of **cutaneous melanoma** in individuals with pathologic involvement of regional lymph nodes if more than 1 mm who have undergone complete resection, including total lymphadenectomy.

Blue Advantage will treat **Yervoy® (ipilimumab)** as a **covered benefit** for the treatment of **metastatic or unresectable melanoma** when used **in combination with Opdivo (nivolumab)** for **any** of the following:

- As first-line therapy; **OR**
- As a second line or subsequent therapy for disease progression for patients with performance status 0-2 if not previously used

Blue Advantage will treat **Yervoy (ipilimumab)** as a **covered benefit** for the treatment of **small cell lung cancer** when used **in combination with Opdivo (nivolumab)** for subsequent systemic therapy in individuals with performance status of 0-2 for **any** of the following:

- Relapse within 6 months following complete or partial response or stable disease with initial treatment; **OR**
- Primary progressive disease

Blue Advantage will treat **Yervoy® (ipilimumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service September 1, 2015 through November 5, 2016
Blue Advantage will treat **Yervoy® (ipilimumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** and the individual does not have an active autoimmune disease.

Blue Advantage will treat **Yervoy® (ipilimumab)** as a **covered benefit** for **retreatment** in adult patients with **unresectable or metastatic melanoma** when ***all*** of the following are met:

- experienced no significant systemic toxicity during prior medically necessary Yervoy (ipilimumab) therapy; **and**
- relapsed after initial clinical response or progressed after stable disease greater than 3 months following completion of prior Yervoy (ipilimumab) therapy

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Melanoma, the most aggressive type of skin cancer, is the leading cause of death from skin cancer. Melanoma is more likely to spread to other parts of the body than other forms of skin cancer and has been on the rise over the past several decades, according to the National Cancer Institute, with an estimated 87,110 new cases and 9,730 deaths from the disease in 2017. In stage III melanoma, the cancer has reached one or more lymph nodes. Patients with stage III melanoma are generally treated by surgery to remove the melanoma skin lesions and the nearby lymph nodes.

Primary treatment of melanoma includes surgical excision and usually involves additional testing to appropriately identify the severity of the disease, also called clinical staging. Melanoma often begins as a single lesion or tumor. If the cancer cells spread from one part of the body to another it is called advanced or metastatic melanoma. Treatment is based on the extent of the disease and may include single agent or combination chemotherapy, radiation therapy, as well as FDA approved biologic agents such as interleukin-2 (IL-2) and interferon alpha.

The United States Food and Drug Administration (FDA) initially approved ipilimumab in March 2011 for treatment of unresectable or metastatic melanoma. This approval was based on a multicenter, randomized, double-blind phase III trial in which 676 subjects with previously treated metastatic melanoma were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus

gp100 peptide vaccine (403 subjects), ipilimumab alone (137), or gp100 vaccine alone (136). Participants were treated every 3 weeks for a total of 4 treatments. Repeat treatment with ipilimumab (re-induction) was permitted in those with progressive disease who previously had stable disease or complete or partial remission. The primary endpoint was overall survival (OS). All study subjects had received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2. Other inclusion criteria were age at least 18 years, life expectancy of at least 4 months, ECOG performance status of 0 or 1, positive status for HLA-A*201, normal hematologic, hepatic, and renal function, and no systemic treatment in the previous 28 days. Exclusion criteria included primary ocular melanoma and untreated metastases in the central nervous system. Both ipilimumab groups showed statistically significant improved survival rates when compared with the gp100 vaccine alone. There was no statistically significant difference in OS between the two ipilimumab groups. The OS rates for ipilimumab plus gp100 vaccine, ipilimumab alone, and gp100 vaccine alone were 21.6%, 23.5%, and 13.7%, respectively at 24 months. Ipilimumab improved survival independent of age, sex, baseline serum lactate dehydrogenase levels, stage of metastasis, and use or non-use of interleukin-2 therapy.

At a 2 plus year follow-up of the Hodi trial, McDermott and colleagues analyzed 474 of the 676 originally randomized subjects. Survival rates at 2 and 3 years were 25% (24 of 95) and 25% (13 of 53) with ipilimumab alone and 19% (54 of 284) and 15% (24 of 156) with ipilimumab plus gp100. Safety among persons with survival of at least 2 years was comparable with the overall study population, with the onset of new ipilimumab-related toxic effects reported in 6 of 78 (8%) of cases. The authors reported that ipilimumab therapy was associated with survival of at least 2 years in approximately one-fifth of qualifying participants enrolled in the study.

In addition to the pivotal study above, there is an additional phase III randomized clinical trial and multiple reports of phase II randomized clinical trials which demonstrate the efficacy of ipilimumab in the treatment of unresectable or metastatic melanoma.

Robert and colleagues described the safety and efficacy data obtained from the subgroup of subjects retreated with ipilimumab in the pivotal phase III study previously described. Of the 676 original participants, 32 had a partial or complete response or stable disease post-treatment and met eligibility criteria for retreatment. However, a total of 40 subjects actually received retreatment. A majority of those (34 of 40; 85%) who started a first retreatment cycle received the target number of 4 doses. A second retreatment cycle was started by 7 subjects, and of these 5 (71.4%) received all 4 doses. A third retreatment cycle was started and completed by only 1 subject. Best overall response rates (complete responses plus partial responses) for 31 subjects eligible for retreatment in the ipilimumab plus gp100 and ipilimumab plus placebo groups were 3 of 23 (13.0%) and 3 of 8 (37.5%), respectively. The disease control rate among those retreated with ipilimumab was 65.2% and 75.0% in the ipilimumab plus gp100 and ipilimumab plus placebo groups, respectively. Nineteen of 31 (61.3%) retreated subjects who received ipilimumab survived over 2 years from their initial randomization at study entry. No new types of toxicities occurred during retreatment and most events were mild-to-moderate.

Kelderman and colleagues evaluated baseline serum lactate dehydrogenase (LDH) as a predictive marker for overall metastatic melanoma survival rate. A total of 166 subjects with

advanced cutaneous melanoma were treated in the Netherlands (NL) with ipilimumab. Best overall response and disease control rates were 17% and 35%, respectively. Median follow-up was 17.9 months, with a median progression-free survival of 2.9 months. Median OS was 7.5 months, and OS at 1 year was 37.8% and at 2 years was 22.9%. The findings were validated in an independent cohort of 64 subjects with advanced cutaneous melanoma in the UK. The authors concluded that their results show efficacy of ipilimumab comparable with that reported in the phase III studies and additionally stated:

> In both the NL and UK cohorts, long-term benefit of ipilimumab treatment was unlikely for patients with baseline serum LDH greater than twice the upper limit of normal. In the absence of prospective data, clinicians treating melanoma may wish to consider the data presented here to guide patient selection for ipilimumab therapy.

Larkin and colleagues conducted a multi-center, double-blind, phase 3 study of 945 previously untreated subjects with histologically confirmed unresectable stage III or IV melanoma randomized to nivolumab alone, nivolumab and ipilimumab, or ipilimumab alone. Eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, age at least 18 years, measurable disease as assessed by computed tomography or magnetic resonance imaging, and a BRAF V600 mutation status. Of the individuals enrolled in the study, 316 were assigned to nivolumab, 314 to nivolumab and ipilimumab, and 315 to ipilimumab only. The coprimary end points of the study were progression-free survival (PFS) and overall survival (OS). In the nivolumab group, median PFS was 6.9 months as compared to 11.5 months in the nivolumab-plus ipilimumab group, and 2.9 months in the ipilimumab group. Rates of objective responses as assessed by investigators were 43.7% for nivolumab only, 57.6% for nivolumab and ipilimumab, and 19% for the ipilimumab group. Time to an objective response was similar in all 3 groups and the median duration of response was not reached in any group. Treatment related adverse events of any grade were observed in 82.1% of subjects treated with nivolumab only, 95.5% of subjects treated with nivolumab and ipilimumab, and in 86.2% of those in the ipilimumab group. The authors concluded that longer PFS and higher rates of objective response occurred with nivolumab alone and the combination of nivolumab and ipilimumab versus ipilimumab alone. Additionally noted was that "the management of adverse events with combination therapy suggests that it can be used safely in a broad range of clinical settings."

Postow and colleagues conducted a double blind study of 142 previously untreated subjects with metastatic melanoma. Inclusion criteria for the study included the presence of histologically confirmed, unresectable, previously untreated stage III or IV melanoma with measurable disease, a known BRAF V600 mutation status, an ECOG performance-status score of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability), and the availability of tumor tissue from a metastatic or unresectable site for immune histochemical assessment. Key exclusion criteria were active brain metastases, uveal melanoma, and serious autoimmune disease .Randomization occurred at a 2:1 ratio, and subjects were assigned to either ipilimumab (3 mg per kilogram of body weight) combined with either nivolumab (1 mg per kilogram) or placebo once every 3 weeks for 4 doses, followed by nivolumab (3 mg per kilogram) or placebo every 2 weeks until disease progression or unacceptable toxic effects. The primary end point was the rate of investigator-assessed, confirmed objective response among individuals with BRAF V600 wild-type tumors. Confirmed objective response occurred in 61%

of subjects (44 of 72) with BRAF wild type tumors that received both ipilimumab and nivolumab (combination group) versus 11% (4 of 37 subjects) in the group that received ipilimumab and placebo (ipilimumab monotherapy group). In the combination group, complete response occurred in 16 subjects (22%) and there were no complete responses achieved in the ipilimumab monotherapy group. Neither group reached the median duration of response. The median progression-free survival was not reached with the combination therapy and was 4.4 months with ipilimumab monotherapy. Similar results for response rate and progression-free survival were observed in 33 subjects with BRAF mutation–positive tumors. Grade 3 or 4 drug related adverse events occurred in 54% of subjects who received the combination therapy as compared to 24% who received ipilimumab monotherapy.

The authors concluded that ipilimumab plus nivolumab combination therapy resulted in:

> "..durable responses and a substantially higher objective response rate, longer progression-free survival, and higher rates of complete response than ipilimumab monotherapy among patients with BRAF wild-type advanced melanoma and those with BRAF-mutant advanced melanoma."

The NCCN Drugs and Biologics Compendium (2016) indicates that for unresectable or metastatic disease, ipilimumab may be used with nivolumab as first-line therapy, or as a single drug or with nivolumab as second-line or subsequent treatment if the individual has disease progression and a performance status of 0-2, if not previously used. Additionally, NCCN indicates that ipilimumab may be used as a single-agent for re-induction therapy in certain individuals who did not have significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease greater than 3 months.

Adjuvant Treatment of Cutaneous Melanoma

On October 28, 2015 the FDA expanded their approval of ipilimumab with the additional indication of adjuvant treatment of individuals with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. This approval was based on a randomized, double-blind, placebo-controlled phase 3 trial of individuals with resected Stage IIIA (> 1 mm nodal involvement), IIIB, and IIIC (with no in-transit metastases) histologically confirmed cutaneous melanoma who had not received previous systemic therapy for melanoma. Between July of 2008 and August of 2011, a total of 951 individuals with a median age of 51 years from 91 hospitals located in 19 countries were randomly assigned to either ipilimumab (n=475) or placebo (n=476). Complete resection of melanoma with full lymphadenectomy within 12 weeks prior to randomization was required for enrollment. Those with prior therapy for melanoma, autoimmune disease, and prior or concomitant use of immunosuppressive agents were excluded. Of the enrollees, 94% had an ECOG performance status of 0. At a median follow-up of 2.74 years there were 528 recurrence-free survival events (234 in the ipilimumab group and 294 in the placebo group). Median recurrence-free survival was 26.1 months in the ipilimumab group and 17.1 months in the placebo group. At 3 years, the recurrence-free survival was 46.5% in the ipilimumab group versus 34.8% in the placebo group. The most common grade 3-4 immune-related adverse events in the ipilimumab group were gastrointestinal, hepatic, and endocrine. Treatment was discontinued in 245 (52%) of 471 subjects who started ipilimumab during the

initial treatment period due to adverse events. A total of 5 subjects died due to drug-related adverse events in the ipilimumab group. The authors concluded that adjuvant ipilimumab significantly improved recurrence-free survival for subjects with completely resected high-risk stage III melanoma and the adverse event profile was consistent with that observed in advanced melanoma.

Primary ocular melanoma is treated with radiation, enucleation (eye removal) or transscleral resection depending on the size and location of the tumor.

Treatment of Melanoma with Brain Metastases
A 2012 phase II trial studied the safety and efficacy of ipilimumab in individuals with melanoma and brain metastases. A total of 72 subjects were enrolled in the study and divided into 2 parallel cohorts; 51 into cohort A and 21 into cohort B. Individuals in cohort A were neurologically asymptomatic and not receiving corticosteroid treatment at study entry, while those in cohort B were symptomatic and on a stable dose of corticosteroids. After 12 weeks, 9 subjects in cohort A demonstrated disease control as did 1 subject in cohort B. The assessment of the brain alone demonstrated that 12 subjects in cohort A (24%) and 2 in cohort B (10%) achieved disease control. Disease control outside of the brain was observed in 14 subjects (27%) in cohort A and in 1 subject (5%) in cohort B. Common adverse grade 3 events in cohort A were diarrhea and fatigue and in cohort B, were dehydration, hyperglycemia, and increased serum aspartate aminotransferase concentrations. One subject in each cohort had grade 4 confusion. The authors concluded that ipilimumab has activity without unexpected negative effects in some individuals with advanced melanoma and brain metastases, especially when metastases were small and asymptomatic.

The NCCN Drugs and Biologics Compendium (2017) indicates that ipilimumab may be considered as single-agent treatment for brain metastases if active against primary tumor (melanoma) for recurrent disease, and as single-agent treatment if active against primary tumor (melanoma) for brain metastases in persons with recurrent stable systemic disease.

Small Cell Lung Cancer
Neuroendocrine tumors account for approximately 20% of lung cancers, most are small cell lung cancer (SCLC). In 2016, an estimated 31,000 new cases of SCLC will occur in the United States. SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. Most patients with SCLC present with hematogenous metastases; approximately one third present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die of recurrent disease.

The updated NCCN clinical practice guidelines in oncology include category 2A recommendation for the use of nivolumab and nivolumab plus ipilimumab as options for subsequent therapy for patients who have relapsed 6 months or less after primary therapy. These off-label recommendations are based on phase 1/2 trial in which patients received either nivolumab with or without ipilimumab for relapsed SCLC. Response rates were 10% (10/98) for nivolumab 3mg/kg, 23% (14/61) for nivolumab 1mg/kg plus ipilimumab 3mg/kg, and 19% (10/54) for nivolumab 3mg/kg plus ipilimumab 1mg/kg. Diarrhea was the most common grade 3

or 4 treatment-related adverse event. The overall frequency of grade 3 or 4 adverse events was about 20%, and less than 10% of patients discontinued treatment because of treatment- related adverse events.

Key Words:

Metastatic melanoma, cutaneous melanoma, Yervoy, ipilimumab, Opdivo, nivolumab, small cell lung cancer, SCLC

Approved by Governing Bodies:

Yervoy, administered intravenously, was originally approved in 2011 to treat late-stage melanoma that cannot be removed by surgery. Yervoy is a monoclonal antibody that blocks a molecule known as CTLA-4 (cytotoxic T-lymphocyte antigen). CTLA-4 may play a role in slowing down or turning off the body's immune system, and affects its ability to fight off cancerous cells. Yervoy may work by allowing the body's immune system to recognize, target and attack cells in melanoma tumors.

On October 28, 2015, the U.S. Food and Drug Administration expanded the approved use of Yervoy (ipilimumab) to include a new use as adjuvant therapy for patients with stage III melanoma, to lower the risk that the melanoma will return following surgery.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

J9228	Injection, ipilimumab, 1 mg

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Medical Policy Group, October 2017
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