BlueCross BlueShield of Alabama

Name of Policy:
Yervoy™ (Ipilimumab)

Policy #: 335
Category: Pharmacology

Latest Review Date: October 2013
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) located in the skin. Metastatic melanoma is the deadliest form of the disease, and occurs when cancer spreads beyond the surface of the skin to other organs, such as the lymph nodes, lungs, brain or other areas of the body. Melanoma is mostly curable when treated in its early stages. However, in its late stages, the average survival rate is approximately six months with a one-year mortality rate of 75 percent. According to the National Cancer Institute, an estimated 68,130 new cases of melanoma were diagnosed in the U.S. during 2010 and about 8,700 people died from the disease.

Yervoy™ (ipilimumab) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody approved by the FDA on March 25, 2011 for the treatment of unresectable or metastatic melanoma. CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. Ipilimumab's mechanism of action in patients with melanoma is indirect, possibly through T-cell mediated anti-tumor immune responses. Yervoy™ is administered as an intravenous infusion over 90 minutes and the recommended dosage regimen is 3mg/kg every three weeks for a total of four doses.

Policy:

Yervoy™ (ipilimumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of adult patients with unresectable or metastatic melanoma.

Yervoy™ (ipilimumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for **reinduction** 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 Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate 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:

Initial treatment

The safety and efficacy of YERVOY were investigated in a randomized (3:1:1), double-blind, double-dummy study (Study 1) that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive YERVOY at 3 mg/kg in combination with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100), 137 were randomized to receive YERVOY at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only patients with HLA-A2*0201 genotype; this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The study excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation. YERVOY/placebo was administered at 3 mg/kg as an intravenous infusion every three weeks for four doses. Gp100/placebo was administered at a dose of 2 mg peptide by deep subcutaneous injection every three weeks for four doses. Assessment of tumor response was conducted at weeks 12 and 24, and every three months thereafter. Patients with evidence of objective tumor response at 12 or 24 weeks had assessment for confirmation of durability of response at 16 or 28 weeks, respectively.

The major efficacy outcome measure was overall survival (OS) in the YERVOY+gp100 arm compared to that in the gp100 arm. Secondary efficacy outcome measures were OS in the YERVOY+gp100 arm compared to the YERVOY arm, OS in the YERVOY arm compared to the gp100 arm, best overall response rate (BORR) at week 24 between each of the study arms, and duration of response.

Of the randomized patients, 61%, 59%, and 54% in the YERVOY+gp100, YERVOY, and gp100 arms, respectively, were men. Twenty-nine percent were ≥65 years of age, the median age was 57 years, 71% had M1c stage, 12% had a history of previously treated brain metastasis, 98% had ECOG performance status of 0 and 1, 23% had received aldesleukin and 38% had elevated LDH level. Sixty-one percent of patients randomized to either YERVOY-containing arm received all four planned doses. The median duration of follow-up was 8.9 months.

The best overall response rate (BORR) as assessed by the investigator was 5.7% (95% CI: 3.7%, 8.4%) in the YERVOY+gp100 arm, 10.9% (95% CI: 6.3%, 17.4%) in the YERVOY arm, and 1.5% (95% CI: 0.2%, 5.2%) in the gp100 arm. The median duration of response was 11.5 months in the YERVOY+gp100 arm and has not been reached in the YERVOY or gp100 arm.

Retreatment/Reinduction therapy

Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) that has been shown to improve survival in patients with pretreated, advanced melanoma in a Phase III trial. Some patients in this study who initially responded to ipilimumab treatment but later progressed were eligible for retreatment with their original randomized regimen. In the study by Robert et al outcomes for these patients concerning baseline characteristics, best overall response, and disease control rate were assessed and considered with respect to the overall study population. In the Phase III study, 676 pretreated patients were randomly allocated to treatment with ipilimumab 3 mg/kg plus gp100 vaccine, ipilimumab 3 mg/kg plus placebo, or gp100 vaccine alone. Of those patients, 32 had a partial or

complete objective response or stable disease after treatment and met the eligibility criteria for retreatment, although a total of 40 patients were retreated. Best overall response rates (complete responses plus partial responses) for 31 retreatment-eligible patients in the ipilimumab plus gp100 and ipilimumab plus placebo groups was three of 23 (13.0%) and three of eight (37.5%), respectively, and disease control rates were 65.2% and 75.0%. No new types of toxicities occurred during retreatment and most events were mild-to-moderate. Ipilimumab provided durable objective responses and/or stable disease in qualifying patients who received retreatment upon disease progression with a similar toxicity profile to that seen during their original treatment regimen.

Key Words:

Yervoy™, ipilimumab, metastatic melanoma

Approved by Governing Bodies:

Yervoy™ (Bristol-Myers Squibb) was FDA approved March 25, 2011 for the treatment of patients with unresectable (inoperable) or metastatic melanoma.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.
Pre-certification requirements: Not applicable.

Current Coding:

HCPCS Codes:

J9228 Injection, Ipilimumab, 1 mg **(Effective 01/01/2012)**

Previous Coding:

HCPCS Codes:

J3590 Unclassified biologics **(for use prior to 01/01/2012)**

References:

1. Robert C, Schadendorf D, Messina M, et al. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control. Clin Cancer Res 2013; 19:2232.
2. Yervoy™ (ipilimumab), Full U.S. Prescribing Information and Medication Guide, www.yervoy.com.

Policy History:

Medical Policy Group, May 2011 **(1)**
Medical Policy Administration Committee, May 2011
Available for comment May 25 – July 11, 2011
Medical Policy Group, December 2011 **(1):** Update to Coding section with new code J9228
Medical Policy Group, October, 2013 **(1):** Clarification and separation of policy statement criteria pertaining to "additional doses" of ipilimumab to now be addressed as "reinduction" therapy; no change in coverage
Available for comment October 11 through November 25, 2013
