

Corporate Medical Policy

Ipilimumab (Yervoy)

File Name:	ipilimumab_yervoy
Origination:	6/2011
Last CAP Review:	3/2018
Next CAP Review:	3/2019
Last Review:	4/2018

Description of Procedure or Service

Melanoma is a serious form of skin cancer that develops in the skin cells (melanocytes). Melanoma is the sixth most common cancer in the United States, and the number of melanoma cases diagnosed annually is increasing faster than for many other forms of cancer.

If detected early melanoma can be cured, usually with surgical excision. However when the disease has spread to other parts of the body, the ability to treat becomes increasingly difficult. In late stages of melanoma, the average survival rate is about 6 months with a 1-year mortality rate of 75%, making it one of the most aggressive forms of cancer.

Several chemotherapy drugs have been used to treat metastatic melanoma including dacarbazine, cisplatin, temozolomide and paclitaxel. Immunotherapy using Interlukin-2 has also been used as a treatment for metastatic melanoma. The high dosage rate of Interlukin-2 often leads to toxicity and severe side effects. In March 2011, the FDA approved ipilimumab (Yervoy), a new immune system stimulant as a treatment for unresectable or metastatic melanoma. Ipilimumab is a T-cell potentiator that specifically blocks the inhibitory signal of CTLA-4 (cytotoxic T-lymphocyte associated antigen 4), a molecule on T-cells that plays a vital role in regulation of the body's natural immune response. Suppression of CTLA-4 can improve the immune system's T-cell response. Ipilimumab can be used alone or in combination with a peptide vaccine or other chemotherapy agents.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for Ipilimumab (Yervoy) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

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When Ipilimumab (Yervoy) is covered

Ipilimumab is considered medically necessary for the following conditions:

1. Unresectable or metastatic melanoma, with or without nivolumab (Opdivo); **OR**
2. As 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; **OR**
3. As subsequent systemic therapy in combination with nivolumab (Opdivo) for patients with small cell lung cancer who have relapsed 6 months or less after primary therapy (NCCN 2A); **OR**
4. As treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab (Opdivo); **AND**
5. Ipilimumab will not be used in combination with pembrolizumab (Keytruda); **AND**
6. The patient has not been previously treated with a PD-1 inhibitor.

Use of Ipilimumab (Yervoy) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

When Ipilimumab (Yervoy) is not covered

Ipilimumab is not covered in combination with Vemurafenib (Zelboraf) unless the member is enrolled in a clinical trial.

Ipilimumab (Yervoy) is considered investigational when used for:

1. Non-cancer indications; **OR**
2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under “When Ipilimumab (Yervoy) is covered.”

Policy Guidelines

Recommended dosage for unresectable or metastatic melanoma is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses.

Recommended dosage for adjuvant melanoma is 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 or until documented disease recurrence or unacceptable toxicity.

Recommended dosage for advanced renal cell carcinoma is nivolumab (Opdivo) 3 mg/kg administered intravenously over 30 minutes followed by ipilimumab (Yervoy) 1 mg/kg administered intravenously over 30 minutes on the same day, every 3 weeks for a maximum of 4

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doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks, administered intravenously over 30 minutes.

Permanently discontinue ipilimumab (Yervoy) for severe adverse reactions.

According to the manufacturer's safety information, Yervoy can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of Yervoy.

The FDA approved Ipilimumab on March 25, 2011, with a Risk Evaluation and Mitigation Strategy, which requires a black box warning regarding the immune-mediated adverse reactions as well as the implementation of a communication plan for health care providers. An assessment of the communication plan will be reviewed by the FDA at 18 months, 3 year and 7 year intervals.

Ipilimumab is currently being studied in a number of clinical trials for other clinical indications including, prostate cancer, non-small-cell lung cancer, neuroblastoma, histiocytoma of the bone, and pancreatic cancer. There is also a planned clinical trial proposed to investigate the effectiveness of combining Vemurafenib (Zelboraf) with the Ipilimumab. This study is not yet open for participant recruitment.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), "Investigational (Experimental) Services."

Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: J9228, S0353, S0354

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

National Comprehensive Cancer Network (NCCN) Guidelines Version 4.2011 Melanoma.
Retrieved on May 23, 2011 from
http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf

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Food and Drug Administration (FDA). BLA Approval and REMS for Yervoy (Ipilimumab), 3/25/11. Retrieved on May 22, 2011 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377_REMS.pdf

National Institutes of Health (NIH). Clinical Trial NCT00094653. MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients With Melanoma. Retrieved on May 22, 2011 from <http://clinicaltrials.gov/ct2/show/NCT00094653?term=nct00094653&rank=1>

Hodi FS, O'Day SJ, McDermott DF et al.(2010) Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med. 2010;363:711-23.

Callahan MK, Wolchok JD, Allison JP. Anti-CTLA-4 Antibody Therapy: Immune Monitoring During Clinical Development of a Novel Immunotherapy. Semin Oncol. 2010 Oct;37(5):473-84. Retrieved on May 22, 2011 from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3008567/?tool=pubmed>

Wolchok JD, Weber JS, Hamid O, Lebbé C, et al. Ipilimumab efficacy and safety in patients with advanced melanoma: a retrospective analysis of HLA subtype from four trials. Cancer Immun. 2010 Oct 20;10:9. Retrieved on May 23, 2011 from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964017/?tool=pubmed>

National Institutes of Health (NIH). Clinical Trial NCT01194271. Neoadjuvant Ipilimumab in Prostate Cancer. Retrieved on May 23, 2011 from <http://clinicaltrials.gov/ct2/show/NCT01194271?term=ipilimumab&rank=5>

National Institutes of Health (NIH). Clinical Trial NCT 00836407. Ipilimumab +/- Vaccine Therapy in Treating Patients With Locally Advanced, Unresectable or Metastatic Pancreatic Cancer. Retrieved on May 23, 2011 from <http://clinicaltrials.gov/ct2/show/NCT00836407?term=ipilimumab&rank=7>

Medical Director review 6/2011

Specialty Matched Consultant Advisory Panel 1/2012

Specialty Matched Consultant Advisory Panel – 3/2013

Specialty Matched Consultant Advisory Panel – 3/2014

Specialty Matched Consultant Advisory Panel – 3/2015

Specialty Matched Consultant Advisory Panel- 3/2016

Medical Director review 8/2016

Specialty Matched Consultant Advisory Panel- 3/2017

Specialty Matched Consultant Advisory Panel- 3/2018

U.S. Food and Drug Administration (FDA). Yervoy (ipilimumab) injection. Highlights of prescribing information. April 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125377s073lbl.pdf. Last accessed April 2018.

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National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2018 Small Cell Lung Cancer. Available at: http://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed on March 28, 2018.

Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicenter, open-label, phase ½ trial. *Lancet Oncol* 2016;17:883-895. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27269741>.

Policy Implementation/Update Information

- 6/21/11 New policy implemented. Ipilimumab (Yervoy) is considered medically necessary for the treatment of unresectable or metastatic melanoma. Medical Director review 6/2011. Notification given 7/1/11 for effective date 9/27/11. (mco)
- 9/13/11 Notification policy updated to include the following statements: “Ipilimumab is not covered in combination with Vemurafenib (Zelboraf) unless the member is enrolled in a clinical trial. Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions.” Updated Policy Guidelines. (mco)
- 12/30/11 Deleted codes J3590, C9284 from “Billing/Coding” section and added J9228, which will be effective 1/1/2012. (mco)
- 2/7/12 Specialty Matched Consultant Advisory Panel review 1/2012. No changes to Policy Statements. (mco)
- 4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. No Change to policy. (btw)
- 4/15/14 Specialty Matched Consultant Advisory Panel review 3/25/2014. No Change to policy. (btw)
- 4/28/15 Specialty matched consultant advisory panel review 3/25/2015. No change to policy. (lpr)
- 4/29/16 Updated the “When Covered” section for consistency with BRAF changes. No change to policy statement or intent. Specialty Matched Consultant Advisory Panel review 3/30/2016. Medical Director review. (lpr)
- 12/30/16 Medical Director review 8/2016. No change to policy statement. Added HCPCS codes S0353 and S0354 to Billing/Coding section. Notification given 12/30/16 for effective date 4/1/17. (lpr)
- 4/28/17 Added the following statement to “When Covered” section: “Use of Ipilimumab (Yervoy) may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR** In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached”. Under “When Not Covered” section, added the statement “Ipilimumab (Yervoy) is considered investigational when used for: 1)Non-cancer indications; **OR** 2) When criteria are not met regarding FDA labeling **OR** strong endorsement/ support by nationally recognized compendia, as stated under “When Ipilimumab (Yervoy) is covered.” Added the following statements under “Policy Guidelines” section: 1)Drugs prescribed for treatment of cancer in accordance with FDA label may be

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considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services.” 2) Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia. Medical director review 3/2017. Specialty Matched Consultant Advisory Panel review 3/29/17. No change to policy statement. (lpr)

- 4/27/18 Added the following indications to “When Covered” section: “As subsequent therapy in combination with nivolumab (Opdivo) for patients with small cell lung cancer who have relapsed 6 months or less after primary therapy (NCCN 2A); OR As treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab (Opdivo); AND”. Updated “Policy Guidelines” section to include additional dosing recommendations. Minor typographical changes made to “Description of Procedure or Service” section. Added references. Specialty Matched Consultant Advisory Panel review 3/28/18. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.