BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Cetuximab (Erbitux®)

File Name:	cetuximab_erbitux
Origination:	4/2019
Last CAP Review:	8/2020
Next CAP Review:	8/2021
Last Review:	8/2020

Description of Procedure or Service

Cetuximab (Erbitux®, ImClone Systems) is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. RAS proteins are G proteins that cycle between active (RAS-GTP) and inactive (RAS-GDP) forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways. The *KRAS* gene can harbor oncogenic variants that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. *KRAS* variants are found in approximately 30% to 50% of CRC tumors and are common in other tumor types. Another proto-oncogene that acts downstream from *KRAS*–*NRAS* harbors oncogenic variants in codons 12, 13, or 61 that result in constitutive activation of the EGFR mediated pathway. These variants are relatively rare compared with *KRAS*, detected in perhaps 2% to 7% of CRC specimens. It is unclear whether *NRAS* variants predict poor response to anti-EGFR monoclonal antibody therapy or are prognostic of poor CRC outcome in general. A third proto-oncogene, *BRAF*, encodes a protein kinase and is involved in intracellular signaling and cell growth and is a principal downstream effector of *KRAS*. *BRAF* variants occur in less than 10% to 15% of CRCs and appear to be a marker of poor prognosis. *KRAS* and *BRAF* variants are considered to be mutually exclusive.

Cetuximab (Erbitux) is an EGFR antagonist that was approved by the U.S. Food and Drug Administration (FDA) in February 2004. It is indicted for the treatment of head and neck cancer, as well as *KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer. Cetuximab is not indicated for the treatment of *RAS*-mutant colorectal cancer or when the results of the *RAS* mutation tests are unknown.

Related Policies:
KRAS, NRAS, and BRAF Mutation Analysis in Colorectal Cancer AHS-M2026
Panitumumab (Vectibix®)

******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 cetuximab (Erbitux) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

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.

When Cetuximab (Erbitux) is covered

Cetuximab (Erbitux®) is considered medically necessary for the treatment of patients with:

Colorectal Cancer

- *KRAS* wild-type, EGFR-expressing, metastatic colorectal cancer, as determined by FDA-approved tests when:
  a. Genetic mutation analysis for *RAS* (*KRAS* and *NRAS*) has been performed confirming the tumor tissue genotype is negative for *KRAS* and *NRAS* mutations and documentation has been provided; AND
  b. Cetuximab will be used in combination with FOLFIRI for first line treatment; OR
  c. In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; OR
  d. As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan and cannot tolerate intensive therapy.

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy, **OR**
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil, **OR**
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Limitation of use: Erbitux is not indicated for treatment of *RAS*-mutant colorectal cancer or when the results of the *RAS* mutation tests are unknown.

Use of cetuximab (Erbitux) 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 Cetuximab (Erbitux) is not covered

Cetuximab (Erbitux) is considered **investigational** and therefore not covered when the above criteria are not met.

Cetuximab (Erbitux) 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 Cetuximab (Erbitux) is covered."

Policy Guidelines

EGFR (epidermal growth factor receptor) is overexpressed in colorectal cancer. Randomized trials of EGFR–targeted therapy with monoclonal antibody, cetuximab, have shown clear survival benefit in patients with metastatic colorectal cancer and squamous cell carcinoma of the head and neck. Studies of colorectal cancer showed his benefit to be dependent upon lack of KRAS mutations.

Cetuximab (Erbitux) is administered by intravenous (IV) infusion. The recommended dosing regimen is an initial dose of 400 mg/m^2 as a 120-minute IV infusion followed by 250 mg/ m^2 weekly infused over 60 minutes.

Patients should receive premedication with an IV histamine-1 (H_1) receptor antagonist 30-60 minutes prior to the first dose or subsequent doses as necessary. In addition, cetuximab should be initiated one week prior to start of radiation therapy, and administration should also be completed 1 hour prior to irinotecan, platinum-based therapy with fluorouracil or FOLFIRI.

According to the National Comprehensive Cancer Network (NCCN) Guidelines, wild-type *KRAS* and *BRAF* have been associated with both improved prognosis and increased lymph node retrieval. Determination of tumor gene status for *RAS* (*KRAS*/*NRAS*) mutations are recommended in all patients with metastatic colorectal cancer. Per NCCN recommendations, patients with any known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, as these patients have virtually no likelihood of benefit and the exposure to toxicity and expense in comparison cannot be justified.

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.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J9055, 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

ImClone, LLC. Erbitux (cetuximab) injection for intravenous use. Highlights of prescribing information. June 2018. Available at: http://pi.lilly.com/us/erbitux-uspi.pdf. Accessed April 2019.

Sorich MJ, Wiese MD, Rowland A, et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol. 2015; 26(1):13-21.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Colon Cancer, version 1.2019. Revised March 15, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed April 2019.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Head and Neck Cancers, version 1.2019. Revised March 6, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed April 2019.

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Medical Director review 4/2019

Specialty Matched Consultant Advisory Panel 8/2019

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Colon Cancer, version 4.2019. Revised November 8, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 2019.

Medical Director review 12/2019

Specialty Matched Consultant Advisory Panel 8/2020

Policy Implementation/Update Information

4/30/19 New policy developed. Erbitux is considered medically necessary for the treatment of head and neck cancer and colorectal cancer when specific criteria are present. Added HCPCS codes J9055, S0353, and S0354 to Billing/Coding section. References added. Medical Director review 4/2019. (krc)

10/1/19 Specialty Matched Consultant Advisory Panel review 8/21/2019. No change to policy intent. (krc)

12/10/19 Added the following criteria to "When Covered" section: "genetic mutation analysis for *RAS* (*KRAS* and *NRAS*) has been performed confirming the tumor tissue genotype is negative for *KRAS* and *NRAS* mutations and documentation has been provided; AND". Updated Policy Guidelines with NCCN Guidelines recommendations for determination of tumor gene status for *RAS* (*KRAS*/*NRAS*) mutations in all patients with metastatic colorectal cancer. Reference added. Medical Director review 12/2019. (krc)

10/1/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No change to policy intent. (krc)

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.