

Corporate Medical Policy

Panitumumab (Vectibix[®])

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Origination:	4/2019
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Description of Procedure or Service

Panitumumab (Vectibix[®], Amgen) 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.

Panitumumab (Vectibix) is an EGFR antagonist that was approved by the U.S. Food and Drug Administration (FDA) in September 2006. It is indicated for the treatment of wild-type *RAS* (defined as wild-type in both *KRAS* and *NKRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC) to be used in combination with FOLFOX as first-line treatment or as monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. Panitumumab is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

Related Policies:

KRAS, NRAS, and BRAF Mutation Analysis in Colorectal Cancer AHS-M2026
Cetuximab (Erbix[®])

*****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.**

Panitumumab (Vectibix®)

Policy

BCBSNC will provide coverage for panitumumab (Vectibix) 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 Panitumumab (Vectibix) is covered

Panitumumab (Vectibix®), an EGFR antagonist, indicated for treatment of wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA approved test for this use), is considered medically necessary for the treatment of patients with metastatic colorectal cancer (mCRC) when:

- 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**
- Panitumumab will be used in combination with FOLFOX for first-line treatment, **OR**
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.

Limitation of use: Vectibix is not indicated for the treatment of patients with *RAS*-mutant mCRC or for whom *RAS* mutation status is unknown.

Use of panitumumab (Vectibix) 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 Panitumumab (Vectibix) is not covered

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

Panitumumab (Vectibix) 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 Panitumumab (Vectibix) is covered."

Panitumumab (Vectibix®)

Policy Guidelines

EGFR (epidermal growth factor receptor) is overexpressed in colorectal cancer. EGFR–targeted therapy with monoclonal antibody, panitumumab, has shown survival benefit in patients with metastatic colorectal cancer, however, this benefit is dependent upon lack of variants in certain genes in the signaling pathway downstream from EGFR.

Panitumumab (Vectibix) is administered by intravenous (IV) infusion. The recommended dose is 6 mg/kg every 14 days as an IV infusion over 60 minutes (\leq 1000 mg) or 90 minutes ($>$ 1000 mg).

The infusion rate should be reduced by 50% for the duration of the infusion in patients experiencing a mild or moderate (grade 1 or 2) infusion reaction. The infusion should be terminated in patients experiencing severe infusion reactions, and depending on severity and/or persistence of the reaction, panitumumab may be permanently discontinued.

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 panitumumab or cetuximab, 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.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J9303, 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

Amgen Inc. Vectibix (panitumumab) injection for intravenous use. Highlights of prescribing information. June 2017. Available at: https://www.pi.amgen.com/~media/amgen/repositorysites/pi-amgen-com/vectibix/vectibix_pi.ashx. Accessed April 2019.

Panitumumab (Vectibix®)

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. Rectal Cancer, version 1.2019. Revised March 15, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.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. Vectibix is considered medically necessary for the treatment of patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS*) metastatic colorectal cancer. Added HCPCS codes J9303, 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)
- 9/22/20 Specialty Matched Consultant Advisory Panel review 8/19/2020. No change to policy intent. (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.