Department:	Pharmacy	**Original Approval:**	01/20/2016
Policy #:	PM127	**Last Approval:**	06/14/2018
Title:	Oncology – Vectibix® (panitumumab solution for intravenous infusion)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Panitumumab (Vectibix): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Prescribed by or in consultation with an oncologist -Labs/diagnostics -Medication list (current and past) to include start and end dates of all chemotherapy regimens -Dosing and duration requested -Weight.

BACKGROUND

Vectibix is a fully human monoclonal antibody that binds specifically to the epidermal growth factor receptor (EGFR).[1] *KRAS* and *NRAS* are related members of the *RAS* oncogene family. Signal transduction through the EGFR can result in activation of wild-type *RAS* proteins. However, in cells with activating *RAS* somatic mutations, the resulting mutant *RAS* proteins are continuously active regardless of EGFR regulation. The EGFR plays a key role in activation of the signaling pathways involved in the pathogenesis of CRC and is often overexpressed in mCRC.[2] Vectibix blocks EGFR action and is not effective if downstream signaling pathways are activated independent of EGFR. Detecting mutations that lead to activation of signaling pathways downstream from EGFR can predict resistance to therapy with Vectibix in CRC.

Vectibix is indicated for the treatment of wild-type *KRAS* (exon 2 in codons 12 or 13) metastatic colorectal cancer (mCRC) as determined by a FDA-approved test as follows: as first-line therapy in combination with FOLFOX (5-fluorouracil [5-FU], leucovorin, oxaliplatin) and 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.

Vectibix is available as 100 mg/5 mL, 200 mg/10 mL, and 400 mg/20 mL single-use vials. Vectibix should be administered as an intravenous infusion via infusion pump.

DEFINITIONS

None.

INDICATIONS/CRITERIA

MediCAID Members	***Continue to criteria for approval below.***
MediCARE Members	

Coverage of Vectibix is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Colorectal Cancer.

Criteria. *Patient must meet the following criteria (A, B, C, D, and E)*:

- **A)** Vectibix is prescribed by or in consultation with an oncologist; AND
- **B)** Patient has advanced or metastatic disease; AND
- **C)** The patient's tumor or metastases are wild-type *KRAS* and/or *NRAS* (that is, the tumor or metastases are *KRAS* and/or *NRAS* mutation negative); AND
- **D)** If Vectibix is being used for first-line treatment of metastatic colorectal cancer, the primary tumor originated on the left side of the colon (from splenic flexure to rectum);[2-3] AND
- **E)** Patient meets ONE of the following criteria (i, ii, or iii):
  - **i.** Vectibix will be used in combination with FOLFOX[1-4] (5-fluorouracil [5-FU], leucovorin, oxaliplatin) or FOLFIRI[2-3] (5-FU, leucovorin, irinotecan); OR
  - **ii.** The patient has disease progression on or following fluoropyrimidine- (5-FU, capecitabine [Xeloda® tablets, generics]), oxaliplatin-, or irinotecan-containing chemotherapy regimens; OR
  - **iii.** Vectibix will be used as a single agent because the patient is not an appropriate candidate for intensive therapy.

The National Comprehensive Cancer Network (NCCN) colon cancer guidelines (version 2.2017) recommendations for use of Erbitux® (cetuximab solution for intravenous infusion) and Vectibix are the same, and all of these recommendations are for use in tumors expressing *KRAS/NRAS* wild-type gene.[2] Erbitux or Vectibix is recommended as initial therapy for tumors (*KRAS/NRAS* wild-type gene only and left-sided tumors only) for unresectable advanced or metastatic disease in combination with FOLFOX or FOLFIRI regimens in patients who can tolerate intensive therapy (category 2A) or as a single agent in patients who cannot tolerate intensive therapy (category 2B). Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based therapy) that was used.[2-3]

Some other recommended uses for Erbitux or Vectibix (all of these are for tumors expressing *KRAS/NRAS* wild-type gene only) are as follows:

- as primary treatment in combination with irinotecan or with FOLFIRI for patients with unresectable metachronous metastases who received previous adjuvant FOLFOX or CapeOX (capecitabine and oxaliplatin) within the past 12 months,
- as subsequent therapy for unresectable advanced or metastatic disease not previously treated with Erbitux or Vectibix for one of the following:
  - in combination with irinotecan or with FOLFIRI after first progression (for disease previously treated with oxaliplatin-based therapy without irinotecan);

- in combination with irinotecan after first progression (for disease previously treated with irinotecan-based therapy without oxaliplatin),
- in combination with irinotecan after second or subsequent progression if previously treated with oxaliplatin- and irinotecan-based therapies, or
- in combination with irinotecan if previously treated with FOLFOXIRI (5-FU, leucovorin, oxaliplatin, and irinotecan).

The NCCN rectal cancer guidelines (version 3.2017) recommendations for use of Erbitux or Vectibix are similar to those for colon cancer, especially in the treatment of metastatic disease.[3] Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon and only refers to use of Erbitux or Vectibix as first-line therapy for metastatic disease.[2] If Vectibix or Erbitux is used as initial therapy, then neither Vectibix nor Erbitux should be used in second or subsequent lines of therapy.[2-3] There are no data on switching to either Erbitux or Vectibix after failing on the other drug, and the NCCN panel does not recommend switching once one of these agents has failed. Administration of Vectibix seems feasible for patients who experience severe infusion reactions to Erbitux.[2] Vectibix or Erbitux should not be used as adjuvant therapy for Stage II or III CRC outside the setting of a clinical trial.

In patients with wild-type *KRAS/NRAS* who experience progression on therapies that did not include an EGFR inhibitor, Erbitux or Vectibix plus irinotecan, Erbitux or Vectibix plus FOLFIRI, or single-agent therapy with Erbitux or Vectibix is recommended. In patients with wild-type *KRAS/NRAS* who progress on therapies that did contain an EGFR inhibitor, an EGFR inhibitor is not recommended in subsequent lines of therapy.

The NCCN guidelines also indicate that a sizable body of literature has demonstrated that a mutation in codons 12 or 13 of exon 2 of the *KRAS* gene are essentially insensitive to EGFR inhibitors, such as Erbitux or Vectibix.[2-3] Mutations in *KRAS* outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit from Erbitux or Vectibix therapy. The NCCN panel strongly recommends *RAS* (*KRAS* exon 2 and non-exon 2 and *NRAS)* and *BRAF* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with mCRC *at the time of diagnosis of Stage IV disease*. The recommendation for *KRAS* and *NRAS* testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting, but rather, this early establishment of *KRAS/NRAS* status is appropriate in order to plan for the treatment continuum, so that the information may be obtained in a non-time-sensitive manner, and the patient and provider can discuss the implications of a *KRAS* or *NRAS* mutation, if present, while other treatment options still exist. Because anti-EGFR agents are not used in the management of Stage I, II, or III disease, *KRAS* and *NRAS* genotyping of colorectal cancer is not recommended at these early stages. *KRAS* mutations are early events in colorectal cancer formation, and therefore there is a very tight correlation between mutation status in the primary tumor and the metastases. For this reason, *KRAS* and *NRAS* genotyping can be done on archived specimens of either primary tumor or metastasis. Fresh biopsies should not be obtained solely for the purpose of *KRAS* and *NRAS* genotyping unless an archived specimen from either the primary tumor or metastasis is unavailable. Patients with known codon 12 or 13 *KRAS* mutations should not be treated with either Erbitux or Vectibix, either alone or in combination with other anticancer agents, as there is virtually no chance of benefit. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either Erbitux or Vectibix. Evidence increasingly suggests that *BRAF V600E* mutation makes response to Erbitux and Vectibix highly unlikely as a single agent or in combination with cytotoxic chemotherapy. *KRAS, NRAS,* and *BRAF* mutations are almost always mutually exclusive (that is, mutations in only 1 of the 3 genes occur within any individual tumor).[2-3,5]

The American Society of Clinical Oncology (ASCO) published (2016) a provisional clinical opinion on testing for *RAS* gene mutations in patients with mCRC to predict response to anti-EGFR monoclonal antibody therapy.[6] In this

publication ASCO indicates that all patients with mCRC who are candidates for anti-EGFR antibody therapy should have their tumor tested in a Clinical Laboratory Improvement Amendments certified laboratory for mutations in both *KRAS* and *NRAS* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146). The weight of current evidence indicates that anti-EGFR monoclonal antibody therapy should only be considered for treatment of patients whose tumor is determined to not have mutations detected after such extended *RAS* testing.

Dosing in Metastatic Colorectal Cancer. *Dosing must meet the following:* 6 mg per kg intravenous infusion every 14 days.[1]

The recommended dose of Vectibix for mCRC is 6 mg/kg administered as an intravenous infusion over 60 minutes every 14 days.[1] If the first infusion is tolerated, subsequent infusion are given over 30 to 60 minutes. Doses higher than 1,000 mg should be administered over 90 minutes. This dosing is also recommended in the NCCN colon cancer guidelines.[2]

Note: Dose modifications are recommended for the management of infusion reactions and dermatologic toxicity and may include reducing the infusion rate, stopping the infusion, permanently discontinuing Vectibix, or withholding the dose(s), and are determined by the prescribing physician. See the prescribing information for more detail.

Initial Approval/Extended Approval.

- **A)** *Initial Approval:* Approve 6 months of therapy.
- **B)** *Extended Approval:* Approve at additional 6-month intervals if the patient does not have disease progression, as determined by the prescribing physician.

Duration of Therapy in Metastatic Colorectal Cancer. Indefinite if the patient does not have disease progression, as determined by the prescribing physician.

Labs/Diagnostics. Detection of *KRAS* and *NRAS* mutational status in colorectal tumors or metastases prior to starting therapy with Vectibix is necessary for selection of patients appropriate for Vectibix therapy. See criteria above.

Other Uses with Supportive Evidence

2. **Patient has been Started on Vectibix.** Approve if the patient meets the conditions for coverage required for **Dosing**, **Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for an approved use in this *Vectibix Utilization Review* policy.

3. **Other Cancer Indications.** Forward to the Medical Director for review on a case-by-case basis. The *NCCN Compendium* only includes recommendations for use of Vectibix in colon and/or rectal cancer.[7]

Waste Management for All Indications.
Weight-based dosing is used; the dose should be calculated and the number of vials needed assessed.

Conditions Not Recommended for Approval

Other Indications (Non-Cancer). Coverage is not recommended for circumstances not listed in the Authorization Criteria (FDA-approved indications and Other Uses with Supportive Evidence). Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References

1. Vectibix® injection for intravenous infusion [prescribing information]. Thousand Oaks, CA: Amgen Inc; June 2017.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2017 – March 13, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 14, 2017.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 3.2017 – March 13, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 11, 2017.
4. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase 3 study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol.* 2014;25:1346-1355.
5. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol.* 2010;11:753-762.
6. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal

	growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J Clin Oncol*. 2016;34:179-185. 7. The NCCN Drugs and Biologics Compendium. © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 9, 2017. Search term: panitumumab. **OTHER REFERENCES UTILIZED** • Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med.* 2013;369:1023-1034. • Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol.* 2014;15:569-579. • Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:1065-1075.
CFR	
WAC	WAC 284-43-2050
RCW	
Contract Citation	☒ WAH ☒ IMC ☒ MA
Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
01/12/2017	No revisions	Fran McGaugh
01/13/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM138 to PM127	Cindy Bush
04/27/2018	Transferred to new template	Cindy Bush
05/22/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee