Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM115	**Last Approval:**	05/10/2018
Title:	Cetuximab (Erbitux®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Cetuximab (Erbitux): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Medication list (current and past) to include start and end dates of previous trials for all chemotherapy regimens -Documentation that medication is being prescribed by or in consultation with oncologist -Labs -Dosing and duration requested -Weight -Height -Initial/Extended Approval -Diagnosis.

BACKGROUND

Erbitux is a chimeric monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR).[1] 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] Erbitux 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 Erbitux in CRC. Overexpression of EGFR and/or common ligands have been reported in > 90% of SCCHN.[6]

Erbitux is indicated for the treatment of KRAS wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) as determined by Food and Drug Administration (FDA)-approved tests for the following uses: in combination with FOLFIRI (irinotecan, 5-fluorouracil [5-FU], leucovorin) for first-line treatment; in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; and as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.[1] 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. Erbitux is also indicated in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN); in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN; and as a single agent in patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

Erbitux is available as 100 mg/50 mL, single-use vials and 200 mg/100 mL single-use vials as a sterile, injectable liquid containing no preservatives. Erbitux should be administered as an intravenous infusion via infusion pump or syringe pump.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

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

Food and Drug Administration (FDA)-Approved Indications

1. **Colorectal Cancer**.

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

- **A.** Erbitux 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 Erbitux 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.** Erbitux will be used in combination with FOLFOX (5-fluorouracil [5-FU], leucovorin, oxaliplatin) or FOLFIRI (5-FU, leucovorin, irinotecan);[2-3] OR
  - **ii.** The patient has disease progression on or following fluoropyrimidine- (5-FU, capecitabine), oxaliplatin-, or irinotecan-containing chemotherapy regimens; OR

Erbitux 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 and Vectibix® (panitumumab solution for intravenous infusion) 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.[2-3] 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 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* and *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 or Vectibix highly unlikely as a single agent or in combination with cytotoxic chemotherapy.[2] *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).[2-4]

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.[5] 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 ONE of the following (A OR B):*[1-3]

- **A.** 400 mg per m^2 intravenous infusion followed by 250 mg per m^2 intravenous infusion weekly;[1-2] OR
- **B.** 500 mg per m^2 intravenous infusion every 2 weeks.[2-3]

The approved initial dosing of Erbitux for colorectal cancer is 400 mg/m^2 administered as a 120-minute intravenous infusion.[1] The recommended subsequent weekly dose is 250 mg/m^2 infused over 60 minutes until disease progression or unacceptable toxicity. However, the NCCN colon cancer guidelines also indicate that Erbitux may be given as a 500 mg/m^2 intravenous infusion over 2 hours every 2 weeks.[2] Premedication with an H1 antagonist (e.g., 50 mg of diphenhydramine) intravenously 30 to 60 minutes before the first dose is recommended.[1] Premedication may be given for subsequent doses.

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 Erbitux, or reducing the dose, 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 Erbitux is necessary for selection of patients appropriate for Erbitux therapy. See criteria above.

2. **Head and Neck Squamous Cell Carcinoma (HNSCC).**

Criteria. *Patient must meet the following criteria (A AND B)*:

- **A.** Erbitux is prescribed by or in consultation with an oncologist; AND
- **B.** Patient meets ONE of the following criteria (i, ii, or iii):
  - **i.** Erbitux will be used in combination with radiation therapy; OR
  - **ii.** Erbitux will be used in combination with platinum-based therapy (e.g., cisplatin, carboplatin), OR
  - **iii.** Erbitux will be used as a single agent in patients who have failed prior platinum-based therapy (i.e., cisplatin, carboplatin).

The NCCN head and neck cancers guidelines (version 2.2017) indicate that for very advanced head and neck cancer (metastatic disease at initial presentation or for recurrent or persistent disease with distant metastases) participation in clinical trials is preferred for all patients.[6] One of the standard therapies is a platinum agent plus 5-FU plus Erbitux (category 1 recommendation) in patients with performance status (PS) of 0 to 1. The standard therapy for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy (category 1). Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (i.e., sequential chemoradiotherapy [chemoRT]). After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone vs. radiotherapy plus weekly carboplatin or Erbitux is among the options. For *non-nasopharyngeal*, recurrent, unresectable , or metastatic disease with no surgery or radiotherapy option, combination therapies that include Erbitux are as follows: cisplatin or carboplatin with 5-FU and Erbitux (category 1), cisplatin plus Erbitux, cisplatin or carboplatin with either docetaxel or paclitaxel plus Erbitux; for *nasopharyngeal* disease carboplatin and Erbitux are options. Erbitux is also recommended as a single agent for *non-nasopharyngeal* disease. In newly diagnosed patients with advanced disease, Erbitux with concurrent radiotherapy is recommended for squamous cell cancers of the oropharynx, hypopharynx, or larynx (category 1).

Dosing in Head and Neck Squamous Cell Carcinoma. *Dosing must meet the following:*
400 mg per m^2 intravenous infusion followed by 250 mg per m^2 intravenous infusion weekly.[1]

The approved initial dosing of Erbitux for SCCHN is 400 mg/m^2 administered 1 week prior to initiation of a course of radiation therapy or on the day of initiation of platinum-based therapy with 5-FU as a 120-minute intravenous infusion.[1] The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 infused over 60 minutes for the duration of radiation therapy or until disease progression or unacceptable toxicity when given in combination with platinum-based therapy with 5-FU. As monotherapy, the initial dose is a 400 mg/m^2 intravenous infusion followed by subsequent weekly doses of 250 mg/m^2 until disease progression or unacceptable toxicity.

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 Erbitux, or reducing the dose, and are determined by the prescribing physician. See the prescribing information for more detail.

Initial Approval/Extended Approval.

- **A.** *Initial Approval:* Initial approval is for 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 Head and Neck Squamous Cell Carcinoma. Indefinite if the patient does not have disease progression, as determined by the prescribing physician.

Labs/Diagnostics. None required.

Other Uses with Supportive Evidence

3. Non-Small Cell Lung Cancer (NSCLC).

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

- **A.** Erbitux is prescribed by or in consultation with an oncologist; AND
- **B.** The patient has advanced or metastatic non-small cell lung cancer (NSCLC); AND
- **C.** The patient has progressive disease after receiving at least ONE of the following tyrosine kinase inhibitors: Tarceva® [erlotinib tablets], Iressa® [gefitinib tablets], or Gilotrif® (afatinib tablets); AND
- **D.** Testing is negative for epidermal growth factor receptor *(EGFR) T790M* mutation; AND
- **E.** Erbitux will be used in combination with Gilotrif® (afatinib tablets).

The NCCN guidelines on NSCLC (version 8.2017) indicate that Erbitux may be considered in combination with Gilotrif as subsequent therapy for metastatic disease (adenocarcinoma [mixed subtypes], squamous cell carcinoma, large cell) in patients with a known sensitizing *EGFR* mutation who are *EGFR T790M* negative, have progressed on EGFR tyrosine kinase inhibitor therapy, and have multiple symptomatic systemic lesions (category 2A).[7] In patients with *EGFR* mutation-positive tumors, first-line tyrosine kinase inhibitors are Tarceva, Gilotrif, or Iressa (all category 1). Tagrisso® (osimertinib tablets) is recommended in patients who progress on EGFR tyrosine kinase inhibitor therapy and test positive for *EGFR T790M* mutation.

In one multicenter, Phase 1b trial conducted in the US and the Netherlands, patients (n = 126) with *EGFR*-mutant lung cancer with acquired resistance to Tarceva or Iressa received oral Gilotrif 40 mg daily plus Erbitux 500 mg/m^2 intravenously every 2 weeks.[8] Patients were heavily pretreated with 52% (n = 65/126) having received ≥ 2 lines of therapy; 79% of patients had received cytotoxic chemotherapy in addition to Tarceva or Iressa. At baseline, the *EGFR* mutation status was as follows: Deletion 19 positive (n = 78), L858R positive (n = 41); and other (n = 4). *T790M* mutation status was available in 124 patients with 71 patients being *T790M* positive and 53 patients being *T790M* negative. The rate of confirmed overall response was 29% (n = 37/126) with all being partial responses; 18% of patient had ≥ 50% tumor

shrinkage from baseline. There was no significant difference in overall response rate between patients harboring *T790M*-positive and *T790M*-negative tumors (32% vs. 25%, respectively; P = 0.341). Median duration of response was 5.7 months.

Dosing in NSCLC. *Dosing must meet the following:*
500 mg per m^2 intravenous infusion every 2 weeks.[8]

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 Erbitux, or reducing the dose, 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, as determined by the prescribing physician.

Duration of Therapy in NSCLC. Indefinite as determined by the prescribing physician.

Labs/Diagnostics.
Testing for *EGFR T790M* mutational status is required prior to starting therapy with Erbitux for NSCLC.

4. **Patient has been started on Erbitux.** 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 *Erbitux Utilization Review* policy.

5. **Other Cancer Indications.** Forward to the Medical Director for review on a case-by-case basis. Examples of other indications supported in the *NCCN Compendium*, with category 2A recommendations, include: squamous cell skin cancer, and penile cancer.[9]

Waste Management for All Indications.
Dosing is based on body surface area (m^2); 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. Erbitux® injection for intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly and Company/ImClone LLC; October 2016.
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 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 August 11, 2017.
4. 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.
5. 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.
6. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (Version 2.2017 – May 8, 2017). © 2016 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 14, 2017.
7. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 8.2017 – July 14, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on August 15, 2017.
8. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov*. 2014;4:1036-1045.
9. 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: cetuximab.	
CFR		
WAC	284-43-2050	
RCW		
Contract Citation	☐ WAH	
	☐ IMC	
	☐ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
06/15/2017	Updated Indications and references	Sonya Ou, Pharm.D.
07/24/2017	Formatted in current approved template	Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM125 to PM115	Cindy Bush
4/25/2018	Revision	Jennifer Farley, PharmD
05/10/2018	Approval	UM Pharmacy Subcommittee