Medical Drug Clinical Criteria

Subject:	Erbitux (cetuximab)		
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Overview

This document addresses the use of Erbitux (cetuximab). Erbitux is a recombinant human/mouse chimeric monoclonal antibody that targets and inhibits the biologic activity of the human epidermal growth factor receptor (EGFR). It is primarily used to treat colorectal cancer and squamous cell carcinoma of the head and neck (SCCHN).

The FDA approved indications of Erbitux for SCCHN include use in combination with radiation therapy for initial treatment; in combination with chemotherapy for first-line treatment of recurrent locoregional or metastatic disease; and as a single agent for recurrent or metastatic disease in whom prior chemotherapy has failed. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Erbitux. These recommendations include the use as a single agent or in combination therapy with or without radiation for: distant metastases; unresectable locoregional recurrence; resectable locoregional recurrence without prior radiation; and second primary after prior radiation therapy.

Erbitux is also FDA approved to treat metastatic colorectal cancer, in combination with chemotherapy or as a single agent. It is also FDA-approved for combination use with encorafenib for BRAF mutation positive colorectal cancer after prior therapy. Within the guidelines, NCCN recommends that appendiceal adenocarcinoma be treated with chemotherapy according to colon cancer guidelines. Similarly, it is recommended that anal adenocarcinoma, a rare histologic form of anal cancer, may be treated according to guidelines for rectal cancer. Guidelines for squamous cell anal cancer, the most common type of anal cancer, do not currently include Erbitux among recommended treatments. Erbitux has been studied in the adjuvant setting of colon cancer (Alberts 2012); but trial was halted when data from interim analysis did not demonstrate improved disease-free survival. NCCN notes that Erbitux has no role in the adjuvant treatment of colon cancer at this time.

Squamous Cell Carcinoma of the Skin (SCCS) is a type of non-melanoma skin cancer which is typically treated by surgical excision or radiation. NCCN guidelines provide 2A recommendations for Erbitux in more advanced cases of SCCS, specifically: for inoperable positive regional lymph nodes, regional recurrence, or distant metastases. NCCN guidelines for penile cancer notes that 95% of penile cancers originate from squamous cell carcinomas.

EGFR expression is detected in nearly all individuals with SCCHN and testing is not required by either the package insert or NCCN guidelines. For colorectal cancer, the FDA approved indication includes the requirement for confirmed RAS wild-type, EGFR-expressing histology and that Erbitux is not indicated for those with RAS mutations in either KRAS or NRAS or for whom RAS mutation status is unknown. NCCN also notes that research has demonstrated that mutations in the KRAS, and more recently NRAS genes, are a predictive factor for a lack of response to Erbitux therapy for colorectal cancer. Mutations in the BRAF gene cause a cancer signal downstream of the EGFR/RAS pathway. In the presence of BRAF mutations, NCCN notes that response to EGFR inhibitors is very unlikely unless given with a BRAF inhibitor.

Erbitux and Vectibix (panitumumab) are two EGFR antagonists approved by the FDA. There is currently no evidence to support switching to either Erbitux or Vectibix after failure of the other drug and NCCN recommends against this practice. A course of panitumumab discontinued because of adverse reaction (rather than progressive disease), is ***not*** considered prior treatment. Also, if cetuximab is recommended as initial therapy, it should not be used in second or subsequent lines of therapy. In addition, studies have shown that combination with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity, specifically regarding the addition of Erbitux or Vectibix to a bevacizumab-containing regimen (Tol 2009, Hecht 2009). NCCN strongly recommends against the use of therapy involving concurrent combination of an anti-EGFR agent and an anti-VEGF agent.

Erbitux has a black box warning for infusion reactions and cardiopulmonary arrest. Erbitux can cause serious and fatal infusion reactions; immediately interrupt and permanently discontinue for serious infusion reaction. Cardiopulmonary arrest or sudden death occurred in patients with SCCHN receiving Erbitux with radiation therapy or a cetuximab product with platinum-based

therapy and fluorouracil. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux administration.

Definitions and Measures

Adenocarcinoma: Cancer originating in cells that line specific internal organs and that have gland-like (secretory) properties.

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.

BRAF wild-type: The BRAF gene is normal or lacking mutations

Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.
Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Locally advanced cancer: Cancer that has spread only to nearby tissues or lymph nodes.

One line of therapy: Single line of therapy.

Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.

Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

RAS wild-type: KRAS and NRAS genes are normal or lacking mutations

Second Primary: a new primary cancer that occurs in a person who has had cancer in the past.

Unresectable: Unable to be removed with surgery.

Vascular endothelial growth factor (VEGF): A substance made by cells that stimulates new blood vessel formation.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Erbitux (cetuximab)

Requests for Erbitux (cetuximab) may be approved if the following criteria are met:

I. Individual has a diagnosis of colon, rectal, colorectal, appendix or anal adenocarcinoma and the following are met (NCCN 2A):
   A. Individual has advanced or metastatic disease; **AND**
   B. Individual has gene mutation testing done and has one of the following mutations:
      1. RAS wild-type; **OR**
      2. BRAF wild-type; **OR**
      3. Proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease; **OR**
      4. Deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] and are ineligible or progressed on checkpoint inhibitor immunotherapy; **OR**
      5. Polymerase epsilon/delta [POLE/POLD1] and are ineligible or progressed on checkpoint inhibitor immunotherapy;

OR

II. Individual has a diagnosis of unresectable, advanced, or metastatic colorectal cancer and the following are met (Label, NCCN 2A); **AND**
   A. Individual has one of the following mutations:
      1. BRAF V600E; **OR**
      2. KRAS G12C;

   AND
   B. Individual is using as second-line or subsequent-line therapy; **AND**
   C. Individual is using as part of a combination therapy;

OR

III. Individual has a diagnosis of squamous cell carcinoma of the head and neck (SCCHN), and the following are met:
   A. Cetuximab is used in a single line of therapy; **AND**
   B. Cetuximab is used in one of the following indications:
      1. In combination with radiation therapy for locally or regionally advanced disease; **OR**
      2. As a single agent for the treatment of individuals with recurrent or metastatic disease for whom prior platinum-based therapy has failed; **OR**
      3. Treatment for individuals with recurrent unresectable, or metastatic SCCHN; **OR**
      4. As sequential therapy in combination with radiation; **OR**
      5. As a single agent or in combination therapy with or without radiation therapy for any of the following indications (NCCN 2A):
         a. Unresectable, recurrent, or persistent disease; **OR**
         b. Second primary in individuals who have received prior radiation therapy; **OR**
         c. Resectable locoregional recurrence in individuals who have not received prior radiation therapy; **OR**
         d. Distant metastases;

OR

IV. Individual has a diagnosis of squamous cell skin carcinoma ~~and~~ or penile squamous cell carcinoma and the following are met (NCCN 2A):
   A. Individual has unresectable or locally advanced disease, recurrent, or distant metastatic disease; ~~**AND**~~
   ~~B. Cetuximab is used in a single line of therapy;~~

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OR

V. Individual has a diagnosis of recurrent, advanced or metastatic non-small cell lung cancer and the following are met (NCCN 2A);
   A. Individual has one of the following types of non-small cell lung cancer:
      1. Adenocarcinoma; **OR**
      2. Squamous cell carcinoma; **OR**
      3. Large cell carcinoma;

   AND
   B. Individual has one of the following mutations:
      1. EGFR exon 19 deletion; **OR**
      2. EGFR exon 21 L858R; **OR**
      3. EGFR S768I; **OR**
      4. EGFR L861Q; **OR**
      5. EGFR G719X;

   AND
   C. Individual is using in combination with afatinib; **AND**
   D. Individual is using as subsequent therapy.

Requests for Erbitux (cetuximab) may not be approved for the following:

I. All other indications not included above; **OR**
II. In combination with other monoclonal antibodies; **OR**
III. Use as adjuvant therapy after resection for colon cancer; **OR**
IV. Individual has received prior treatment with panitumumab; **OR**
V. Cetuximab is used in combination with anti-VEGF agents (bevacizumab, ziv-aflibercept, or ramucirumab.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9055	Injection, cetuximab, 10 mg [Erbitux]

ICD-10 Diagnosis

C00.0-C06.9	Malignant neoplasm of lip and oral cavity
C09.0-C14.8	Malignant neoplasm of pharynx
~~C00.0-C14.8~~	~~Malignant neoplasm of lip, oral cavity and pharynx~~
~~C17.0-C17.8~~	~~Malignant neoplasm of small intestine~~
C18.0-C20	Malignant neoplasm of colon, rectosigmoid junction, rectum
C21.0-C21.8	Malignant neoplasm of anus and anal canal
C30.0	Malignant neoplasm of nasal cavity
C31.0-C31.1	Malignant neoplasm of maxillary and ethmoidal sinuses
~~C30.0-C32.9~~	~~Malignant neoplasm of nasal cavities, ear, sinuses, larynx~~
C32.0-C32.9	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of main bronchus
~~C39.0~~	~~Malignant neoplasm of upper respiratory tract, part unspecified~~
C44.02	Squamous cell carcinoma of skin of lip
C44.1291-C44.1292	Squamous cell carcinoma of skin of eyelid, including canthus
C44.221-C44.229	Squamous cell carcinoma of skin of ear and external auricular canal
C44.320-C44.329	Squamous cell carcinoma of skin of nose and other/unspecified parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.520-C44.529	Squamous cell carcinoma of anal skin, skin of breast and other part of trunk
C44.621-C44.629	Squamous cell carcinoma of skin of upper limb, including shoulder
C44.721-C44.729	Squamous cell carcinoma of skin of lower limb, including hip
C44.82	Squamous cell carcinoma of overlapping sites of skin
C44.92	Squamous cell carcinoma of skin, unspecified
~~C49.0~~	~~Malignant neoplasm of connective and soft tissue of head, face and neck~~
C60.0-C60.9	Malignant neoplasm of penis
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.5	Secondary malignant neoplasm of large intestine and rectum
C79.2	Secondary malignant neoplasm of skin
~~D00.00-D00.08~~	~~Carcinoma in situ of lip, oral cavity and pharynx~~
~~D02.0~~	~~Carcinoma in situ of larynx~~

Z51.11-Z51.12	Encounter for antineoplastic chemotherapy and immunotherapy
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.810-Z85.819	Personal history of malignant neoplasm of lip, oral cavity and pharynx
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Document History

Revised: 03/10/2025
Document History:

- 03/10/2025 – Select Review: update Squamous cell cancer of skin and penile cancer criteria. Coding Reviewed: Added ICD-10-CM C33, C44.1291-C44.1292. Removed ICD-10-CM C17.0-C17.8, C39.0, C49.0, D00.00-D00.08, D02.0. Removed ICD-10-CM C07-C08.9 from code range C00.0-C14.8 and updated descriptions. Removed ICD-10-CM C30.1 and C31.2-C31.9 from code range C30.0-C32.9 and updated descriptions.
- 09/09/2024 – Select Review: remove NSCLC from may not approve criteria Coding Reviewed: No changes.
- 05/17/2024 – Annual Review: wording and formatting, add colorectal cancer mutations K12C, POLE/MMR, dMMR/MSI-H, SCCHN, add NSCLC, add penile cancer to squamous cell carcinoma, remove anal cancer from do not approve criteria. Coding Reviewed: Added ICD-10-CM C34.00-C34.92, C60.0-C60.9, Z85.118.
- 05/19/2023 – Annual Review: modify colorectal criteria to match NCCN wording. Coding Reviewed: No changes.
- 05/20/2022– Annual Review: Add BRAF-WT in left-sided colon, rectal, colorectal cancer. Coding Reviewed: No changes.
- 11/19/2021 – Select Review: Update criteria to include BRAF positive colorectal cancer in combination with encorafenib. Coding Reviewed: No changes.
- 05/21/2021 – Annual Review: Clarify squamous cell skin cancer to align with NCCN recommendation. Coding Reviewed: No changes.
- 05/15/2020 – Annual Review: Remove small bowel adenocarcinoma from criteria as NCCN no longer recommends this use. Coding Review: Removed ICD-10-dx C17.9
- 08/16/2019 – Annual Review: Update RAS testing requirements to include both KRAS and NRAS per FDA label. Coding Reviewed: No Changes
- 05/17/2019 – Annual Review: First review of cetuximab clinical criteria. Wording and formatting changes for clarity. Clarify use of adjuvant therapy in colon cancer. Clarify NCCN recommendation for squamous cell skin cancer. Add references for off-label uses. Coding reviewed: no changes.

References

1. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer. JAMA. 2012; 307(13):1383-1393.
2. Carthon BC, Ng CS, Pettaway CA, Pagliaro LC. Epidermal growth factor receptor-targeted therapy in locally advanced or metastatic squamous cell carcinoma of the penis. BJU Int. 2014; 113(6):871-877.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2024. URL: http://www.clinicalpharmacology.com. Updated periodically.
4. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Updated periodically.
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009; 27(5):672-680.
7. 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(9):1036-1045.
8. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2024; Updated periodically.
9. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol. 2010; 28(6):911-917.
10. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009; 360(6):563-572.
11. Pirker R, Pereira JR, von Pawel J, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol. 2012; 13(1):33-42.
12. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed February 21, 2025.
    a. Colon Cancer. V1.2024. Revised January 29, 2024.
    b. Head and Neck Cancers. V3.2024. Revised February 29, 2024.
    c. Non-Small Cell Lung Cancer. V3.2024. Revised March 12, 2024.
    d. Penile Cancer. V1. 2024. Revised October 25, 2023.

e. Rectal Cancer. V1. 2024. Revised January 29, 2024.
f. Squamous Cell Skin Cancer. V2.2025. Revised February 7, 2025.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.