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. 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.

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. Conversely, EGFR has not demonstrated predictive value in colorectal cancer; and NCCN recommends that no patient should be considered for or excluded from anti-EGFR therapy based on EGFR test results. 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; but they can be used if 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. 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.

Other Uses

While NCCN also provides 2A recommendations for Erbitux in penile cancer, the literature cited in this recommendation includes one small retrospective chart review (Carthon 2014). Data from prospective studies are recommended. NCCN also provides 2A recommendations for Erbitux in non-small cell lung cancer (NSCLC). The role of Erbitux in this space has been controversial. Literature includes two randomized trials (Pirkier 2009 [FLEX], Lynch 2010 [BMS099]) which studied Erbitux + chemotherapy vs chemotherapy alone in previously untreated advanced NSCLC. One study (FLEX) showed a modestly prolonged overall survival (OS) in the Erbitux

group while the other (BMS099) showed no significant difference in median progression-free survival or OS. NCCN specifically does not recommend the regimen used in the FLEX trial due to concerns around toxicity. In addition, the NCCN guideline states "some oncologists feel that although the FLEX trial results were reported to be statistically significant, they were not clinically significant". NCCN recommends Erbitux in combination with afatinib for advanced disease that has progressed on tyrosine kinase inhibitor therapy. This recommendation is based on one phase 1b open-label study (Janjigian 2014). NCCN guideline for small bowel adenocarcinoma (SBA) notes that cetuximab and panitumumab should not be used to treat SBA due to inconclusive evidence.

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.

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.

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, ~~small bowel,~~ appendix or anal adenocarcinoma and the following are met (Label, NCCN 2A):
   A. Individual has stage IV disease; **AND**
   B. Extended RAS gene mutation testing with an FDA approved test is confirmed and the tumor is determined to be RAS wild-type+; **AND**
   C. Cetuximab is used as a single agent or as part of combination therapy; **AND**
   D. Individual has not received prior treatment with panitumumab*; **AND**
   E. Cetuximab is not used in combination with anti-VEGF agents (bevacizumab, ziv-aflibercept, or ramucirumab); **AND**
   F. Cetuximab is used in a single line of therapy**;
   +**Note**: RAS wild-type means that the KRAS and NRAS genes are normal or lacking mutations

OR

II. Individual has a diagnosis of squamous cell carcinoma of the head and neck (SCCHN), and the following are met:
   A. Individual has not received prior treatment with panitumumab*; **AND**
   B. Cetuximab is not used in combination with anti-VEGF agents (bevacizumab, ziv-aflibercept, or ramucirumab); **AND**
   C. Cetuximab is used in a single line of therapy**; **AND**
   D. Cetuximab is used in one of the following indications:
      1. In combination with radiation therapy, for the initial treatment of 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. In combination with platinum-based therapy with 5-FU (fluorouracil) as first-line treatment for individuals with recurrent locoregional disease or metastatic SCCHN; **OR**
      4. As a single agent or in combination therapy with or without radiation therapy for any of the following indications (NCCN 2A):
         a. Unresectable locoregional recurrence; **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

III. Individual has a diagnosis of squamous cell skin carcinoma, and the following are met (NCCN 2A):
   A. Individual has unresectable regional lymph nodes, regional recurrence, or distant metastatic disease; **AND**
   B. Individual has not received prior treatment with panitumumab*; **AND**
   C. Cetuximab is not used in combination with anti-VEGF agents (bevacizumab, ziv-aflibercept, or ramucirumab); **AND**
   D. Cetuximab is used in a single line of therapy**.

*__Note__: A course of panitumumab discontinued because of adverse reaction (rather than progressive disease), is ***not*** considered prior treatment.
**__Note__: If cetuximab is recommended as initial therapy, it should not be used in second or subsequent lines of 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. Treatment of squamous cell anal carcinoma; **OR**
V. Treatment of non-small cell lung cancer.

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-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-C32.9	Malignant neoplasm of nasal cavities, ear, sinuses, larynx

C39.0	Malignant neoplasm of upper respiratory tract, part unspecified
C44.02	Squamous cell carcinoma of skin of lip
C44.121-C44.129	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
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

Document History

Revised: 05/15/2020
Document History:

- 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.

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    a. Anal Carcinoma. V1.2020. Revised November 19, 2020.
    b. Head and Neck Cancers. V1.2020. Revised February 12, 2020.
    c. Colon Cancer. V2.2020. Revised March 3, 2020.
    d. Penile Cancer. V1. 2020. Revised January 14, 2020.
    e. Squamous Cell Skin Cancer. V1.2020. Revised October 2, 2019.
    f. Small Bowel Adenocarcinoma. V 1.2020. Revised July 30, 2019.
    g. Non-small Cell Lung Cancer. V3.2020. Revised February 11, 2020.
    h. Rectal Cancer. V2.2020. Revised March 3, 2020.

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.