

## Clinical Policy: Cetuximab (Erbix)

Reference Number: CP.PHAR.317

Effective Date: 02/17

Last Review Date: 02/17

[Coding Implications](#)  
[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### Description

The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for cetuximab for injection (Erbix®).

### Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that Erbix is **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Head and Neck Squamous Cell Carcinoma (must meet all):

1. Diagnosis of head and neck squamous cell carcinoma (HNSCC) (see Appendix B for subtypes by location);
2. Meets a or b:
  - a. FDA approved use (must meet one):
    - i. Locally or regionally advanced disease (Stage III/IV) in combination with radiation therapy;
    - ii. Recurrent or metastatic disease progressing after platinum-based therapy;
  - b. Off-label NCCN recommended use:
    - i. For recurrent/persistent, unresectable or metastatic disease (1 or 2):
      - a) In combination with carboplatin;
      - b) As a single agent or in combination with either a) cisplatin or b) fluorouracil (with cisplatin or carboplatin) for any HNSCC subtype except nasopharyngeal cancer (see Appendix B for subtypes by location).

**Approval duration: 3 months**

##### B. Colorectal Cancer (must meet all):

1. Diagnosis of colorectal cancer (CRC);
2. Disease is KRAS or NRAS wild type (i.e., not mutated);
3. Meets a or b:
  - a. FDA approved use:
    - i. Prescribed for metastatic CRC (a, b, or c):
      - a) As primary therapy in combination with FOLFIRI\*;
      - b) As subsequent therapy in combination with irinotecan if refractory to irinotecan-based chemotherapy;
      - c) As subsequent therapy as a single agent (1 or 2):
        - 1) After failing oxaliplatin- and irinotecan-based chemotherapy;
        - 2) If intolerant to irinotecan;
  - b. Off-label NCCN recommended use:

- i. Prescribed for unresectable, metastatic or inoperable CRC (a, b or c):
  - a) As primary therapy;
  - b) As subsequent therapy (1, 2 or 3):
    - 1) If not previously treated with cetuximab or panitumumab;
    - 2) Following primary treatment with chemoradiation or local therapy;
    - 3) For unresectable metastatic disease;
  - c) As adjuvant therapy\*\* (1 or 2):
    - 1) For unresectable metastatic disease that has converted to resectable disease;
    - 2) Following resection and/or local therapy for metastases if (i or ii):
      - i) Member has received previous chemotherapy;
      - ii) Positive for growth on neoadjuvant\*\* chemotherapy;
- ii. Prescribed for rectal cancer in combination with FOLFO\* or FOLFIRI\*, or as a single agent if intensive therapy is not appropriate:
  - a) As primary therapy for disease characterized as (one of the following):
    - 1) T3, N0, M0 (Stage IIA)†;
    - 2) Any T, N1-2, M0 (Stage III)†;
    - 3) T4 (Stage IIB-C, Stage IIIB-C, Stage IV)†;
    - 4) Locally unresectable or inoperable disease with no metastases if resection is contraindicated following neoadjuvant\*\* therapy.

\*FOLFIRI (fluorouracil, leucovorin, irinotecan); FOLFOX (fluorouracil, leucovorin, oxaliplatin).

\*\*Adjuvant therapy (therapy administered after the main treatment to help decrease the risk of cancer recurring); neoadjuvant therapy (therapy given as a first step to shrink a tumor before the main therapy).

†T (primary tumor characteristics); N (regional lymph nodes); M (metastatic disease).

### Approval duration: 3 months

#### C. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

1. The following NCCN recommended uses for Erbitux, meeting NCCN categories 1, 2a, or 2b, are approved per the CP.PHAR.57 Global Biopharm Policy:
  - a. Squamous cell skin cancer;
  - b. Non-small cell lung cancer (NSCLC);
  - c. Penile cancer.

## II. Continued Approval

### A. All Indications (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member has none of the following reasons to discontinue:
  - a. Disease progression or unacceptable toxicity;
  - b. Serious infusion reactions requiring medical intervention and/or hospitalization;
  - c. Severe acneiform rash:
    - i. Recurrence that does not improve after a one-to-two week infusion delay;
    - ii. Fourth recurrence;
  - d. Interstitial lung disease.

**Approval duration: 6 months**

**B. Other diagnoses/indications (must meet 1 or 2):**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy.

**Background**

*Description/Mechanism of Action:*

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. In vitro assays and in vivo animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Signal transduction through the EGFR results in activation of wild-type Ras proteins, but in cells with activating Ras somatic mutations, the resulting mutant Ras proteins are continuously active regardless of EGFR regulation.

In vitro, cetuximab can mediate antibody-dependent cellular cytotoxicity) against certain human tumor types. In vitro assays and in vivo animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

*Formulations:*

Erbix (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid containing no preservatives.

- 100 mg/50 mL, single-use vial, individually packaged in a carton
- 200 mg/100 mL, single-use vial, individually packaged in a carton

*FDA Approved Indications:*

Erbix is an epidermal growth factor receptor (EGFR) antagonist/intravenous formulation indicated for:

- Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with 5-FU.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.
- Colorectal Cancer
  - K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests:
    - In combination with FOLFIRI for first-line treatment,
    - In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
    - As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitation of use: Erbitux is not indicated for treatment of RAS-mutant colorectal cancer.

## **Appendices**

### **Appendix A: Abbreviation Key**

5-FU: Fluorouracil	HNSCC: Head and neck squamous cell carcinoma
EGF: Epidermal growth factor	KRAS: Kirsten rat sarcoma 2 viral oncogene homologue
EGFR: Epidermal growth factor receptor	NRAS: Neuroblastoma RAS viral oncogene homologue
FOLFIRI: Fluorouracil, leucovorin, irinotecan	NSCLC: Non-small cell lung cancer
FOLFOX: Fluorouracil, leucovorin, oxaliplatin	
HER: Human epidermal growth factor receptor	

### **Appendix B: Head and Neck Squamous Cell Cancers by Location\*<sup>5</sup>**

- Paranasal sinuses (ethmoid, maxillary)
- Larynx (glottis, supraglottis)
- Pharynx (nasopharynx, oropharynx, hypopharynx)
- Lip and oral cavity
- Major salivary glands (parotid, submandibular, sublingual)
- Occult primary

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*\*Squamous cell carcinoma, or a variant, is the histologic type in more than 90% of head and neck cancers.*

### **Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9055	Injection, cetuximab, 10 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Policy split from CP.PHAR.182 Excellus Oncology. NCCN off-label recommended uses added. HNSCC subtypes by location outlined at Appendix B. CRC: EGFR testing is removed from the FDA labeled criteria. NRAS wild type (i.e., not mutated) is added to KRAS wild type. Some NCCN colon cancer off-label recommendations are collapsed and combined into a colorectal section with some rectal cancer indications.	01/17	02/17

**References**

1. Erbitux prescribing information. Indianapolis, IN: Eli Lilly and Company; October 2016. Available at <http://uspl.lilly.com/erbitux/erbitux.html>. Accessed January 24, 2017.
2. Cetuximab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 24, 2017.
3. Head and neck cancers (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 24, 2017.
4. Colon cancer (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 24, 2017.
5. Rectal cancer (Version 2.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 24, 2017.

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note: For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**Note: For Medicare members**, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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