# Clinical Policy: Cetuximab (Erbitux)

Reference Number: CP.PHAR.317
Effective Date: 02.01.17
Last Review Date: 11.18
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

Cetuximab (Erbitux®) is an epidermal growth factor receptor (EGFR) antagonist.

## FDA Approved Indication(s)

Erbitux is indicated for treatment of:

- Head and neck cancer (HNSCC)
  - 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 fluorouracil (5-FU)
  - Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy
- Colorectal cancer (CRC)
  - *K-Ras* wild-type, EGFR-expressing, metastatic CRC as determined by an FDA-approved test
    - 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(s) of use: Erbitux is not indicated for treatment of *Ras*-mutant CRC or when the results of the *Ras* mutation tests are unknown.

## Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that Erbitux 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 HNSCC (*see Appendix B for subtypes by location*);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is advanced, recurrent, or metastatic;

5. Request meets one of the following (a or b):
   a. Dose does not exceed an initial dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly thereafter;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**B. Colorectal Cancer** (must meet all)**:**
1. Diagnosis of CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is KRAS or NRAS wild-type (i.e., not mutated);
5. One of the following (a, b, c, or d):
   a. Request is for first-line treatment: Prescribed in combination with FOLFOX (off-label) or FOLFIRI;
   b. Previous treatment with oxaliplatin- and irinotecan-based chemotherapy (e.g., FOLFOXIRI) or member is intolerant to irinotecan;
   c. Previous treatment with an oxaliplatin containing regimen (e.g., FOLFOX, CapeOx): Prescribed in combination with FOLFIRI, irinotecan, or irinotecan with Zelboraf® if BRAF V600E mutation positive (off-label);
   d. Previous treatment with FOLFIRI: Prescribed in combination with irinotecan, or irinotecan with Zelboraf if BRAF V600E mutation positive (off-label);
6. Request meets one of the following (a or b):
   a. Dose does not exceed an initial dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly thereafter;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**C. Non-Small Cell Lung Cancer (off-label)** (must meet all)**:**
1. Diagnosis of metastatic non-small cell lung cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Tumor is positive for a sensitizing EGFR mutation and T790M negative;
5. Disease has progressed on or after an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., Tarceva®, Gilotrif®, or Iressa®);
   **Prior authorization is (or may be) required for EGFR TKI therapies*
6. Prescribed in combination with Gilotrif as subsequent therapy;
   **Prior authorization is (or may be) required for Gilotrif*
7. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**D. Penile Cancer (off-label)** (must meet all)**:**
1. Diagnosis of metastatic penile cancer;

2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member has received prior systemic chemotherapy (e.g., paclitaxel, ifosfamide, cisplatin, 5-FU);
5. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**E. Squamous Cell Skin Cancer (off-label)** (must meet all)**:**

1. Diagnosis of basal cell carcinoma (non-melanoma), squamous cell skin cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member has regional recurrence or distant metastases;
5. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**F. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. All Indications in Section I** (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Erbitux for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
   a. For HNSCC or CRC: New dose does not exceed 250 mg/m$^2$ weekly;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 12 months**

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

5-FU: fluorouracil
CRC: colorectal cancer
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
FOLFIRI: fluorouracil, leucovorin, irinotecan
FOLFOX: fluorouracil, leucovorin, oxaliplatin
FOLFOXIRI: fluorouracil, leucovorin, oxaliplatin, irinotecan
HER: human epidermal growth factor receptor
HNSCC: head and neck squamous cell carcinoma
KRAS: Kirsten rat sarcoma 2 viral oncogene homologue
NRAS: neuroblastoma RAS viral oncogene homologue

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| Modified FOLFOX 6 | **CRC**<br>Day 1: oxaliplatin 85 mg/m$^2$ IV<br>Day 1: Folinic acid 400 mg/m$^2$ IV<br>Days 1–3: 5-FU 400 mg/m$^2$ IV bolus on day 1, then 1,200 mg/m$^2$/day × 2 days (total 2,400 mg/m$^2$ over 46–48 hours) IV continuous infusion<br>Repeat cycle every 2 weeks. | See dosing regimen |
| CapeOX | **CRC**<br>Day 1: Oxaliplatin 130 mg/m$^2$ IV<br>Days 1–14: Capecitabine 1,000 mg/m$^2$ PO BID<br>Repeat cycle every 3 weeks. | See dosing regimen |
| FOLFIRI | **CRC**<br>Day 1: Irinotecan 180 mg/m$^2$ IV<br>Day 1: Leucovorin 400 mg/m$^2$ IV<br>Day 1: Flurouracil 400 mg/m$^2$ IV followed by 2,400 mg/m$^2$ continuous IV over 46 hours<br>Repeat cycle every 14 days. | See dosing regimen |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| FOLFOXIRI | **CRC**<br>Day 1: Irinotecan 165 mg/m$^2$ IV, oxaliplatin 85 mg/m$^2$ IV, leucovorin 400 mg/m$^2$ IV, flurouracil 1,600 mg/m$^2$ continuous IV for 2 days (total 3,200 mg/m$^2$)<br>Repeat cycle every 2 weeks. | See dosing regimen |
| Gilotrif (afatinib) | **Metastatic NSCLC**<br>40 mg PO QD | 40 mg/day; 50 mg/day when on chronic concomitant therapy with a P-gp inducer |
| Iressa (gefitinib) | **Metastatic NSCLC**<br>250 mg PO QD | 250 mg/day; 500 mg/day when used with a strong CYP3A4 inducer |
| Tarceva (erlotinib) | **Metastatic NSCLC**<br>150 mg PO QD | 150 mg/day; 450 mg/day when used with a strong CYP3A4 inducer or 300 mg/day when used with a moderate CYP1A2 inducer |
| TIP (paclitaxel, ifosfamide, cisplatin) | **Penile Cancer**<br>Paclitaxel 175 mg/m$^2$ IV on day 1; ifosfamide 1,200 mg/m$^2$ IV on day 1-3; cisplatin 25 mg/m$^2$ IV on day 1-3<br>Repeat every 3 to 4 weeks. | See dosing regimen |
| 5-FU, cisplatin | **Penile Cancer**<br>5-FU 800 - 1,000 mg/m$^2$/day continuous IV on days 1-4 or 2-5; cisplatin 70-80 mg/m$^2$ IV on day 1<br>Repeat every 3 to 4 weeks. | See dosing regimen |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): none reported
- Boxed warning(s): infusions reactions, cardiopulmonary arrest

*Appendix D: Head and Neck Squamous Cell Cancers by Location**

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

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

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| HNSCC, CRC | Initial dose: 400 mg/m$^2$ IV followed by 250 mg/m$^2$ IV weekly | See dosing regimen |

## VI. Product Availability

Single-dose vials: 100 mg/50 mL, 200 mg/100 mL

## VII. References

1. Erbitux Prescribing Information. Indianapolis, IN: Eli Lilly and Company; June 2018. Available at http://uspl.lilly.com/erbitux/erbitux.html. Accessed July 25, 2018.
2. Cetuximab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed July 25, 2018.

## 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 | P&T Approval Date |
|---|---|---|
| Policy split from CP.PHAR.182 Excellus Oncology.<br>NCCN off-label recommended uses added.<br>HNSCC subtypes by location outlined at Appendix B.<br>CRC: EGFR testing is removed from the FDA labeled criteria.<br>NRAS wild type (i.e., not mutated) is added to KRAS wild type.<br>Some NCCN colon cancer off-label recommendations are collapsed and combined into a colorectal section with some rectal cancer indications. | 01.17 | 02.17 |
| Policy converted to new template. Annual Review.<br>Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs. Criteria with NCCN 2B rating recommendations removed. Added criteria for NCCN 2A or above off-label indications for NSCLC, penile cancer, and squamous cell skin cancer. Authorization limits extended from 3 and 6 months to 6 and 12 months for initial and continued approval, respectively. | 08.30.17 | 11.17 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 4Q 2018 annual review: no significant changes; added Commercial and HIM lines of business; summarized NCCN and FDA-approved uses for improved clarity; added specialist involvement in care; references reviewed and updated | 07.25.18 | 11.18 |

**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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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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.

**For Health Insurance Marketplace members**, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.