# Clinical Policy: Cetuximab (Erbitux)

Reference Number: LA.PHAR.317
Effective Date: 02.03.24
Last Review Date: ~~06.25.23~~05.07.24
Line of Business: Medicaid

Coding Implications
Revision Log

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

****Please note: This policy is for medical benefit****

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

**FDA Approved Indication(s)**
Erbitux is indicated for treatment of:

- ~~Squamous~~Head and neck squamous cell carcinoma ~~of the head and neck (SCCHN~~(HNSCC)
  - Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy for initial treatment
  - Recurrent locoregional disease or metastatic ~~squamous cell carcinoma of the head and neck~~HNSCC in combination with platinum-based therapy with fluorouracil (5-FU) for first-line treatment
  - Recurrent or metastatic ~~squamous cell carcinoma of the head and neck~~HNSCC progressing after platinum-based therapy, as a single agent
- Colorectal cancer (CRC)
  - *K-Ras* wild-type, EGFR-expressing, metastatic CRC as determined by an FDA-approved test
    - In combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) 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
  - *BRAF* V600E mutation-positive metastatic CRC
    - In combination with encorafenib, for the treatment of adult patients with metastatic CRC with a *BRAF* V600E mutation, as detected by an FDA-approved test, after prior therapy

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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 Louisiana Healthcare Connections® that Erbitux is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Head and Neck Squamous Cell Carcinoma ~~of the Head and Neck~~** (must meet all)**:**

1. Diagnosis of ~~SCCHN~~HNSCC (*see Appendix D 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. Prescribed as one of the following (a or b):
   a. As a single agent;
   b. In combination with platinum-based therapy (e.g., cisplatin or carboplatin~~);*~~) or Opdivo®;*
      **Prior authorization may be required for platinum-based therapies.*
6. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed an initial dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly thereafter;
   b. Dose does not exceed 500 mg/m$^2$ every 2 weeks;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**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 one of the following (a, b, or c):
   a. Wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS*);
   b. *BRAF* wild-type;
   c. *BRAF* V600E mutation positive;
5. Member has advanced, unresectable or metastatic CRC and one of the following (a or b):*
   a. Request for use as a single agent or in combination with FOLFIRI, FOLFOX, CapeOX, or irinotecan in the initial or subsequent line setting;
   b. Prescribed in combination with Braftovi® if BRAF V600E mutation positive after prior therapy;

   **Prior authorization may be required*
6. For colon cancer that is *KRAS/NRAS/BRAF* wild-type: colon cancer is left-sided only (*see Appendix E*);

~~6.~~7. Request meets one of the following (a, b, or c):*
   a. Dose does not exceed an initial dose of 400 mg/m$^2$ followed by 250 mg/m$^2$ weekly thereafter;
   b. Dose does not exceed 500 mg/m$^2$ every 2 weeks;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

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**Approval duration: 6 months**

**C. Non-Small Cell Lung Cancer (off-label)** (must meet all)**:**
1. Diagnosis of recurrent, advanced, or 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;
5. Prescribed in combination with Gilotrif as subsequent therapy;*
   **Prior authorization may be required for Gilotrif*
6. One of the following (a or b):
   a. Disease has progressed on or after an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., Tarceva®, Gilotrif®, or Iressa®);*
   b. Tumor is T790M positive and disease has progressed on or after Tagrisso®;*
   **Prior authorization may be required for Tagrisso and EGFR TKI therapies*
7. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**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. Request is for use as a single agent as subsequent-line systemic therapy;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**E. Squamous Cell Skin Cancer (off-label)** (must meet all)**:**
1. Diagnosis of squamous cell skin cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request is for use as a single agent;
5. Disease is ~~locally~~ advanced, high-risk, very high-risk, metastatic, inoperable or not fully resectable;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

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

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1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

**II. Continued Therapy**

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

1. Currently receiving medication via Louisiana Healthcare Connections 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 ~~SCCHN~~HNSCC or CRC: New dose does not exceed 250 mg/m$^2$ weekly or 500 mg/m$^2$ every 2 weeks;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 12 months**

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

**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 policy LA.PMN.53

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

5-FU: fluorouracil
CapeOX: capecitabine, oxaliplatin
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

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~~SCCHN: squamous cell carcinoma of the head and neck~~

*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 |
| 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 |
| Tagrisso® (osimertinib) | **NSCLC**<br>80 mg PO QD | 80 mg/day; 160 mg/day when used with a strong CYP3A inducer |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| erlotinib (Tarceva®) | **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, carboplatin | ~~**SCCHN**~~<br>**HNSCC**<br>cisplatin 100 mg/m2 IV or carboplatin AUC 5 IV on day 1, plus 5-FU 1,000 mg/m$^2$ IV on days 1, 2, 3, and 4, repeated every 3 weeks<br><br>**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 |
| ~~Braftovi® (encorafenib)~~ | ~~**CRC**~~<br>~~300 mg PO once daily in combination with cetuximab (400 mg/m$^2$ IV over 120 minutes on day 1 followed by weekly infusions of cetuximab 250 mg/m$^2$ IV over 60 minutes) until disease progression or unacceptable toxicity.~~ | ~~450 mg/day.~~ |

*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.

*Appendix E: KRAS/NRAS/BRAF Wild-Type Colon Cancer*

- The NCCN Colon Cancer Guidelines recommend that cetuximab should only be used for left-sided tumors. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab. Data on the response to cetuximab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| ~~SCCHN~~HNSCC, CRC | Weekly schedule: initial dose 400 mg/m$^2$ IV followed by 250 mg/m$^2$ IV weekly<br><br>Biweekly schedule: initial and subsequent doses 500 mg/m$^2$ IV every 2 weeks | 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; September 2021. Available at: http://uspl.lilly.com/erbitux/erbitux.html. Accessed ~~August 11, 2022~~July 7, 2023.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August ~~11, 2022~~17, 2023.
3. National Comprehensive Cancer Network. Head and Neck Cancer Version 2.~~2022~~2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed August ~~11, 2022~~17, 2023.
4. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer 3.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August ~~11, 2022~~17, 2023.
5. National Comprehensive Cancer Network. Squamous Cell Skin Cancer ~~2.2022~~1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed August ~~11, 2022~~17, 2023.

## 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.



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| HCPCS Codes | Description |
|---|---|
| J9055 | Injection, cetuximab, 10 mg |

| Reviews, Revisions, and Approvals | Date | LDH Approval Date |
|---|---|---|
| Converted corporate policy to local policy. | 06.25.23 | 01.03.24 |
| Annual review: for HNSCC added combination therapy with Opdivo per NCCN; for CRC added CapeOX as a possible combination therapy per NCCN; for colon cancer that is KRAS/NRAS/BRAF wild-type added criterion that disease is left-sided only per NCCN, along with rationale in Appendix E; for squamous cell skin cancer, removed "locally" from locally advanced disease qualifier as disease can be regional per NCCN; references reviewed and updated. | 05.07.24 | |

**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. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developingthis clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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 LHCC has no control or right of control. Providers are not agents or employees of LHCC.