VENTURA COUNTY
HEALTH CARE PLAN

# UTILIZATION MANAGEMENT MEDICAL POLICY

**POLICY:** Oncology (Injectable) – Erbitux Utilization Management Medical Policy
- Erbitux® (cetuximab intravenous infusion – ImClone/Eli Lilly)

**REVIEW DATE:** 02/26/2025

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## OVERVIEW

Erbitux, an epidermal growth factor receptor (EGFR) chimeric monoclonal antibody, is indicated for the following uses:[1]

- **Colorectal cancer** (CRC), *KRAS* wild-type, EGFR-expressing, metastatic CRC as determined by an FDA-approved test for the following uses:
  - In combination with FOLFIRI (irinotecan, 5-fluorouracil [5-FU], 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.

  Limitation of use: Erbitux is not indicated for treatment of *RAS*-mutant CRC or when the results of the *RAS* mutation tests are unknown.
- **CRC**, metastatic, *BRAF V600E* mutation-positive, as detected by an FDA-approved test, in combination with Braftovi® (encorafenib capsules) for adults after prior therapy.
- **Squamous Cell Carcinoma of the Head and Neck**:
  - In combination with radiation therapy for the initial treatment of locally or regionally advanced disease.
  - In combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional or metastatic disease.
  - As a single agent in patients with recurrent or metastatic disease for whom prior platinum-based therapy has failed.

## Guidelines

Erbitux is addressed in a number of National Comprehensive Cancer Network (NCCN) guidelines:

- **Colon** and **Rectal Cancer:** Guidelines for colon cancer (version 1.2025 – February 7, 2025) recommend Erbitux as initial therapy for advanced or metastatic *KRAS/NRAS/BRAF* wild-type and left-sided tumors only, in combination with FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI, or CapeOX (capecitabine and oxaliplatin) regimens in patients who can tolerate intensive therapy (category 2A) or as a single agent in patients who cannot tolerate intensive therapy (category 2B).[2,6] Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon. Erbitux in combination with Braftovi is recommended for the initial treatment of *BRAF V600E* mutation positive disease (category 2A). For the initial treatment of unresectable synchronous liver and/or lung metastases only, Erbitux in combination with either FOLFIRI or FOLFOX is recommended for *KRAS/NRAS/BRAF* wild-type and left-sided tumors only (category 2A). For the initial treatment of unresectable metachronous metastases, NCCN recommends Erbitux in combination with irinotecan or FOLFIRI for *KRAS/NRAS/BRAF* wild-type and left-sided tumors only; in combination with Braftovi for *BRAF V600E* mutation positive disease; or in combination with Lumakras (sotorasib tablets) or Krazati (adagrasib tablets) for *KRAS G12C* mutation positive tumors (category 2A). Therapies recommended after first progression vary depending on the initial treatment regimen (i.e., 5-FU/leucovorin-based or capecitabine-based

therapy) that was used. The NCCN guidelines recommend Erbitux, in combination with irinotecan, FOLFOX, CapeOX, or FOLFIRI for the subsequent treatment of *KRAS/NRAS/BRAF* wild-type tumors; in combination with Braftovi for the subsequent treatment of *BRAF V600E* mutation positive disease; or in combination with Lumakras or Krazati for *KRAS G12C* positive tumors. The NCCN rectal cancer guidelines (version 1.2025 – February 7, 2025) make the same recommendations for Erbitux for the treatment of rectal cancer.[3,6]

- **Head and Neck Cancer**: Guidelines (version 2.2025 – January 17, 2025) recommend Erbitux in combination with radiation therapy, with a platinum agent (cisplatin or carboplatin) with or without 5-FU, with a platinum agent plus either docetaxel or paclitaxel, with docetaxel or paclitaxel, with Keytruda® (pembrolizumab intravenous infusion) or Opdivo® (nivolumab intravenous infusion), or as a single agent.[4,6]
- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2025 – January 14, 2025) recommend Erbitux in combination with Gilotrif® (afatinib tablets) as subsequent therapy for recurrent, advanced, or metastatic disease in patients with a known sensitizing *EGFR* mutation who have progressed on EGFR tyrosine kinase inhibitor (TKI) therapy, and have multiple symptomatic systemic lesions; or with a known sensitizing EGFR mutation who have progressed on EGFR TKI therapy and have asymptomatic disease, symptomatic brain lesions, or isolated symptomatic lesions.[5,6]
- **Penile Cancer:** Guidelines (version 2.2025 – January 6, 2025) recommend Erbitux as a single agent for the subsequent treatment of patients with recurrent or metastatic disease (category 2A).[6,7]
- **Squamous Cell Skin Cancer:** Guidelines (version 2.2025 – February 7, 2025) recommend Erbitux in combination with radiation therapy for unresectable, inoperable, or incompletely resected regional disease, or metastatic disease; or as systemic therapy alone or in combination with carboplatin and paclitaxel in patients ineligible for or progressed on checkpoint inhibitors with unresectable, inoperable, or incompletely resected regional disease, or regional recurrence or distant metastases.[6,8]

## POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Erbitux. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Erbitux, as well as the monitoring required for adverse events and long-term efficacy, approval requires Erbitux to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Erbitux is recommended in those who meet one of the following criteria:

### FDA-Approved Indications

1. **Colon and Rectal Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):

**i.** Patient has advanced or metastatic disease and meets ONE of the following (a, b, c, or d):
- **a)** Patient meets ALL of the following [(1), (2), (3), and (4)]:
  - **(1)** Tumor or metastases are *KRAS*, *NRAS*, and *BRAF* wild-type; AND
    Note: The tumor or metastases are *KRAS/NRAS/BRAF* mutation negative.
  - **(2)** The primary tumor originated on the left side of the colon; AND
    Note: primary tumor originated from the splenic flexure to the rectum.
  - **(3)** Medication is used for initial treatment; AND
  - **(4)** Medication is used as a single agent or in combination with FOLFOX, CapeOX, or FOLFIRI; OR
    Note: FOLFOX includes 5-fluorouracil; leucovorin, and oxaliplatin; CapeOX included capecitabine and oxaliplatin; and FOLFIRI includes 5-fluorouracil, leucovorin, and irinotecan.
- **b)** Patient meets ALL of the following [(1), (2), and (3)]:
  - **(1)** Tumor or metastases are *KRAS/NRAS/BRAF* wild-type; AND
    Note: The tumor or metastases are *KRAS*, *NRAS*, and *BRAF* mutation negative.
  - **(2)** Medication is used for subsequent treatment; AND
  - **(3)** Medication is used as a single agent or in combination with irinotecan, FOLFOX, CapeOX, or FOLFIRI; OR
    Note: FOLFOX includes 5-fluorouracil; leucovorin, and oxaliplatin; CapeOX included capecitabine and oxaliplatin; and FOLFIRI includes 5-fluorouracil, leucovorin, and irinotecan.
- **c)** Patient meets BOTH of the following [(1) and (2)]:
  - **(1)** Tumor or metastases are *BRAF V600E* mutation-positive; AND
  - **(2)** Medication is used in combination with Braftovi (encorafenib capsules); OR
- **d)** Patient meets ALL of the following [(1), (2), and (3)]:
  - **(1)** Tumor or metastases are *KRAS G12C* mutation positive; AND
  - **(2)** Medication is used for subsequent therapy; AND
    Note: This is subsequent therapy following the initial diagnosis of colon or rectal cancer.
  - **(3)** Medication is used in combination with Lumakras (sotorasib tablets) or Krazati (adagrasib tablets); OR

**ii.** Patient has unresectable synchronous liver and/or lung metastases and meets ALL of the following (a, b, c, and d):
Note: Synchronous metastases are metastases that are diagnosed at the same time as or within a few months of the initial diagnosis of colon or rectal cancer.
- **a)** Metastases are *KRAS/NRAS/BRAF* wild-type; AND
  Note: The metastases are *KRAS*, *NRAS*, and *BRAF* mutation negative.
- **b)** The primary tumor originated on the left side of the colon; AND
  Note: Primary tumor originated from the splenic flexure to the rectum.
- **c)** Medication is used for primary treatment; AND
- **d)** Medication is used in combination with FOLFOX or FOLFIRI; OR
  Note: FOLFOX includes 5-fluorouracil, leucovorin, and oxaliplatin and FOLFIRI includes fluorouracil, leucovorin, and irinotecan.

**iii.** Patient has unresectable metachronous metastases and meets ONE of the following (a, b, or c):
Note: Metachronous metastases are metastases that are diagnosed months to years after the initial diagnosis of colon or rectal cancer.
- **a)** Patient meets ALL of the following [(1), (2), and (3)]:
  - **(1)** Metastases are *KRAS/NRAS/BRAF* wild-type; AND
    Note: The metastases are *KRAS*, *NRAS*, and *BRAF* mutation negative.
  - **(2)** Medication is used for initial treatment; AND
  - **(3)** Medication is used in combination with irinotecan or FOLFIRI; OR

Note: FOLFIRI includes fluorouracil, leucovorin, and irinotecan.

**b)** Patient meets ALL of the following [(1), (2), and (3)]:
- **(1)** Metastases are *BRAF V600E* mutation positive; AND
- **(2)** Medication is used for initial treatment; AND
- **(3)** Medication is used in combination with Braftovi; OR

**c)** Patient meets ALL of the following [(1), (2), and (3)]:
- **(1)** Metastases are *KRAS G12C* mutation positive; AND
- **(2)** Medication is used for initial treatment; AND
- **(3)** Medication is used in combination with Lumakras or Krazati; AND

**C)** Erbitux is prescribed by or in consultation with an oncologist.

**Dosing.** Approve ONE of the following dosing regimens (A or B):

**A)** Approve the following regimen (i and ii):
- **i.** Initial Dose: Approve up to 400 mg/m$^2$ administered by intravenous infusion given once; AND
- **ii.** Maintenance Dose: Approve up to 250 mg/m$^2$ administered by intravenous infusion, given no more frequently than once weekly; OR

**B)** Approve up to 500 mg/m$^2$ administered by intravenous infusion, given no more frequently than once every 2 weeks.

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**2. Head and Neck Squamous Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):

**A)** Patient is ≥ 18 years of age; AND

**B)** Patient meets ONE of the following (i, ii, iii, iv, or v):
- **i.** Erbitux will be used in combination with radiation therapy; OR
- **ii.** Erbitux will be used in combination with platinum-based therapy; OR
  Note: Examples of platinum chemotherapy include cisplatin and carboplatin.
- **iii.** Erbitux will be used in combination with paclitaxel or docetaxel; OR
- **iv.** Erbitux will be used in combination with Keytruda (pembrolizumab intravenous infusion) or Opdivo (nivolumab intravenous infusion); OR
- **v.** Erbitux will be used as a single agent; AND

**C)** Erbitux is prescribed by or in consultation with an oncologist.

**Dosing.** Approve ONE of the following dosing regimens (A or B):

**A)** Approve the following regimen (i and ii):
- **i.** Initial Dose: Approve up to 400 mg/m$^2$ administered by intravenous infusion, give once; AND
- **ii.** Maintenance Dose: Approve up to 250 mg/m$^2$ administered by intravenous infusion, given no more frequently than once weekly; OR

**B)** Approve up to 500 mg/m$^2$ administered by intravenous infusion, given no more frequently than once every 2 weeks.

**Other Uses with Supportive Evidence**

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**3. Appendiceal Adenocarcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has advanced or metastatic disease and meets ONE of the following (i or ii):
  - **i.** Patient meets BOTH of the following (a and b):
    - **a)** Tumor or metastases are *BRAF V600E* mutation-positive; AND
    - **b)** Medication is used in combination with Braftovi (encorafenib capsules); OR
  - **ii.** Patient meets ALL of the following (a, b, and c):
    - **a)** Tumor or metastases are *KRAS G12C* mutation positive; AND
    - **b)** Medication is used for subsequent therapy; AND
    - **c)** Medication is used in combination with Lumakras (sotorasib tablets) or Krazati (adagrasib tablets); AND
- **C)** Erbitux is prescribed by or in consultation with an oncologist.

**Dosing.** Approve ONE of the following dosing regimens (A or B):
- **A)** Approve the following regimen (i and ii):
  - **i.** Initial Dose: Approve up to 400 mg/m$^2$ administered by intravenous infusion given once; AND
  - **ii.** Maintenance Dose: Approve up to 250 mg/m$^2$ administered by intravenous infusion, given no more frequently than once weekly; OR
- **B)** Approve up to 500 mg/m$^2$ administered by intravenous infusion, given no more frequently than once every 2 weeks.

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**4. Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent, advanced, or metastatic non-small cell lung cancer; AND
- **C)** Patient has a known sensitizing epidermal growth factor receptor *(EGFR)* mutation; AND
  Note: Examples of *EGFR* mutations include *EGFR* exon 19 deletion, or exon 21 *L858R*, or *EGFR S768I, L861Q,* and/or *G719X* mutation positive.
- **D)** Patient has received at least ONE tyrosine kinase inhibitor; AND
  Note: Examples of tyrosine kinase inhibitors include erlotinib tablets, Iressa (gefitinib tablets), or Gilotrif (afatinib tablets).
- **E)** Erbitux will be used in combination with Gilotrif (afatinib tablets); AND
- **F)** Erbitux is prescribed by or in consultation with an oncologist.

**Dosing.** Approve ONE of the following dosing regimens (A or B):
- **A)** Approve the following regimen (i and ii):
  - **i.** Initial Dose: Approve up to 400 mg/m$^2$ administered by intravenous infusion, give once; AND
  - **ii.** Maintenance Dose: Approve up to 250 mg/m$^2$ administered by intravenous infusion, given no more frequently than once weekly; OR
- **B)** Approve up to 500 mg/m$^2$ administered by intravenous infusion, given no more frequently than once every 2 weeks.

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**4. Penile Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has recurrent or metastatic disease; AND

**C)** Erbitux will be used as subsequent therapy; AND
**D)** Erbitux will be used as a single agent; AND
**E)** Erbitux is prescribed by or in consultation with an oncologist.
**Dosing.** Approve the following dosing regimen (A and B):
**A)** Initial Dose: Approve up to 400 mg/m$^2$ administered by intravenous infusion, given once; AND
**B)** Maintenance Dose: Approve up to 250 mg/m$^2$ administered by intravenous infusion, given no more frequently than once weekly.

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**5. Squamous Cell Skin Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
**A)** Patient is ≥ 18 years of age; AND
**B)** Patient meets ONE of the following (i, ii, iii, or iv):
**i.** Patient has locally advanced, high-risk, or very high-risk disease; OR
**ii.** Patient has unresectable, inoperable, or incompletely resected regional disease; OR
**iii.** Patient has local or regional recurrence; OR
**iv.** Patient has distant metastases; AND
**C)** Erbitux is prescribed by or in consultation with an oncologist.

**Dosing.** Approve the following dosing regimen (A and B):
**A)** Initial Dose: Approve up to 400 mg/m$^2$ administered by intravenous infusion, given once; AND
**B)** Maintenance Dose: Approve up to 250 mg/m$^2$ administered by intravenous infusion, given no more frequently than once weekly.

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## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Erbitux is not recommended in the following situations:

**1.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

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3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – February 7, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed February 18, 2025.
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5. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – January 14, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 18, 2025.
6. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on February 18, 2025. Search term: cetuximab.
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13. Janjigian YY, Smit EF, Groen HJM, 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;4:1036-1045.

## HISTORY

| Type of Revision | Summary of Changes | Review Date |
|---|---|---|
| Annual Revision | **Colon and Rectal Cancer:** Patient is ≥ 18 years of age added as additional requirement. Unresectable added as descriptor to patient has unresectable, advanced, or metastatic disease. Clarified 400 mg/m$^2$ dosing regimen: Initial dose is up to 400 mg/m$^2$ administered once, followed by Maintenance dose of up to 250 mg/m$^2$ given no more frequently than once weekly.<br>**Head and Neck Squamous Cell Carcinoma:** Patient is ≥ 18 years of age added as additional requirement. Erbitux will be used in combination with Opdivo (nivolumab intravenous infusion) added as additional option for approval. Clarified 400 mg/m$^2$ dosing regimen: Initial dose is up to 400 mg/m$^2$ administered once, followed by Maintenance dose of up to 250 mg/m$^2$ given no more frequently than once weekly.<br>**Non-Small Cell Lung Cancer (NSCLC):** Patient is ≥ 18 years of age added as additional requirement. Recurrent added as descriptor to patient has recurrent, advanced, or metastatic NSCLC. Exon 21 added as a descriptor in Note. Clarified 400 mg/m$^2$ dosing regimen: Initial dose is up to 400 mg/m$^2$ administered once, followed by Maintenance dose of up to 250 mg/m$^2$ given no more frequently than once weekly.<br>**Penile Cancer:** Patient is ≥ 18 years of age added as additional requirement. Clarified 400 mg/m$^2$ dosing regimen: Initial dose is up to 400 mg/m$^2$ administered once, followed by Maintenance dose of up to 250 mg/m$^2$ given no more frequently than once weekly.<br>**Squamous Cell Skin Cancer:** Patient is ≥ 18 years of age added as additional requirement. Advanced added as descriptor to patient has locally advanced, high-risk, or very high-risk disease. Unresectable added as descriptor to patient has unresectable, inoperable, or incompletely resected regional disease. Clarified 400 mg/m$^2$ dosing regimen: Initial dose is up to 400 mg/m$^2$ administered once, followed by Maintenance dose of up to 250 mg/m$^2$ given no more frequently than once weekly. | 08/02/2023 |
| Annual Revision | **Colon and Rectal Cancer:** Add new option for approval for patients with unresectable synchronous liver and/or lung metastases. Added new option for approval for patients with unresectable metachronous metastases. Removed criterion that the tumor or metastases are wild-type *BRAF* and criterion that the patient has previously received a chemotherapy regimen for colon or rectal cancer. Removed unresectable from criterion that the patient has advanced or metastatic disease and meets one of the following. Added *BRAF* to criterion that the tumor or metastases are *KRAS/NRAS/BRAF* mutation negative; and added medication is for initial therapy and medication is used in combination with FOLFOX, CapeOX, or FOLFIRI to condition of approval. Added condition of approval for the subsequent treatment of *KRAS/NRAS/BRAF* mutation negative disease. Added condition of approval for *BRAF V600E* mutation positive disease. Added condition of approval for *KRAS G12C* mutation positive disease.<br>**Head and Neck Squamous Cell Carcinoma:** Added new option of approval for Erbitux to be used in combination with paclitaxel or docetaxel. Added Keytruda (pembrolizumab intravenous infusion) to option of approval Erbitux will be used in combination with Keytruda (pembrolizumab intravenous infusion) or Opdivo (nivolumab intravenous infusion).<br>**Appendiceal Adenocarcinoma:** Added new condition of approval.<br>**Penile Cancer:** Added recurrent to requirement that the patient has recurrent or metastatic disease. | 08/07/2024 |
| Early Annual Revision | **Colon and Rectal Cancer:** As a single agent added to the requirement that the medication is used as a single agent or in combination with FOLFOX, CapeOX, or FOLFIRI. Removed requirement that the medication is used for subsequent treatment. This is subsequent therapy following the initial diagnosis of colon or rectal cancer added as a Note. Added synchronous metastases are metastases that are diagnosed at the same time as or within a few months of the initial diagnosis of colon or rectal cancer | 02/26/2025 |

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|---|---|---|
| | as a Note. Added metachronous metastases are metastases that are diagnosed months to years after the initial diagnosis of colon or rectal cancer.<br>**Appendiceal Adenocarcinoma:** Medication is used for subsequent treatment removed as a requirement. | |