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: 08/02/2023

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 2.2023 – April 25, 2023) recommend Erbitux as primary therapy for unresectable, advanced, or metastatic *KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only, in combination with irinotecan, FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI, or FOLFOXIRI (5-FU, leucovorin, oxaliplatin, irinotecan) regimens in patients who can tolerate intensive therapy or as a single agent in patients who cannot tolerate intensive therapy.[2,6] Reference to left-sided only disease refers to a primary tumor that originated in the left side of the colon. 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, or FOLFIRI for the subsequent treatment of *KRAS/NRAS/BRAF* wild-type tumors; or in combination with Braftovi for the subsequent treatment of *BRAF V600E* positive disease. The NCCN rectal cancer guidelines (version 3.2023 – May 26, 2023) make the same recommendations for Erbitux for the treatment of rectal cancer.[3,6]
- **Head and Neck Cancer**: Guidelines (version 2.2023 – May 15, 2023) 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, or as a single agent.[4,6]

- **Non-Small Cell Lung Cancer:** Guidelines (version 3.2023 – April 13, 2023) 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 1.2023 – December 1, 2022) recommend Erbitux as a single agent for the subsequent treatment of patients with metastatic disease.[6,7]
- **Squamous Cell Skin Cancer:** Guidelines (version 1.2023 – March 10, 2023) recommend Erbitux as a single agent or in combination with radiation therapy for inoperable or incompletely resected regional disease, or as systemic therapy alone in patients ineligible for checkpoint inhibitors with 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

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1. Colon and Rectal Cancer. Approve for 1 year if the patient meets the following (A, B, C, D, E, and F):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has unresectable, advanced, or metastatic disease; AND
- **C)** Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and *NRAS* wild-type) [that is, the tumor or metastases are *KRAS* and *NRAS* mutation negative]; AND
- **D)** The primary tumor originated on the left side of the colon (from splenic flexure to rectum); AND
- **E)** Patient meets ONE of the following (i or ii):
  - **i.** Patient's tumor or metastases are wild-type *BRAF* (that is, the tumor or metastases are *BRAF V600E* mutation-negative); OR
  - **ii.** Patient's tumor or metastases are *BRAF V600E* mutation-positive and the patient meets BOTH of the following (a and b):
    - **a)** Patient has previously received a chemotherapy regimen for colon or rectal cancer; AND
      Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine, oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
    - **b)** Erbitux is prescribed in combination with Braftovi (encorafenib capsules); 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 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 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.** 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 Opdivo (nivolumab intravenous infusion); OR
- **iv.** 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. Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets 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 the following (A, B, C, D, and E):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has 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 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.

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

1. Erbitux® intravenous infusion [prescribing information]. Indianapolis, IN: Eli Lilly/ImClone; September, 2021.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – April 25, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 24, 2023.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – May 26, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed July 24, 2023.
4. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (version 2.2023 – May 15, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.
5. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.
6. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023. Search term: cetuximab.

7. The NCCN Penile Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – December 1, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.
8. The NCCN Squamous Cell Skin Cancer Clinical Practice Guidelines in Oncology (version 1.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on July 24, 2023.
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11. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol*. 2011;29:3419-3426.
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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	**Non-Small Cell Lung Cancer:** Added Note with examples of epidermal growth factor receptor mutations. **Squamous Cell Skin Cancer:** Added additional condition of approval for patients with local, high-risk or very high-risk disease.	07/27/2022
Selected Revision	**Colon and Rectal Cancer:** Revised "and/or" to "and" in requirement that "Patient's tumor or metastatases are wild-type *RAS* (*KRAS* wild-type and/or *NRAS* wild-type) [that is, the tumor or metastatases are *KRAS* and/or *NRAS* mutation negative]." The requirement "If Erbitux is being used for first line treatment" was removed from "the primary tumor originated on the left side of the colon (from splenic flexure to rectum)."	08/24/2022
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. **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. **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. **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. **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