Utilization Review Policy 157

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

EFFECTIVE DATE: 1/1/2021
LAST REVISION DATE: 11/19/2025

COVERAGE CRITERIA FOR: All Aspirus Medicare Plans

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:

- **Appendiceal Adenocarcinoma:** Guidelines for appendiceal neoplasms and cancers (version 1.2026 – October 30, 2025) recommend Erbitux as second-line and subsequent therapy for advanced or metastatic *KRAS/NRAS/BRAF* wild-type, in combination with FOLFOX (5-FU, leucovorin, oxaliplatin), FOLFIRI, CapeOX (capecitabine and oxaliplatin) or as a single agent (category 2A). Guidelines also recommend Erbitux as initial, second-line, and subsequent therapy for advanced or metastatic *BRAF V600E* mutation positive disease, in combination with Braftovi or FOLFOX (category 2A). Additionally, NCCN recommends Erbitux as second-line and subsequent therapy for advanced or metastatic disease, in combination with Lumakras (sotorasib tablets) or Krazati (adagrasib tablets) for *KRAS G12C* mutation positive tumors (category 2A).

- **Colon Cancer:** Guidelines for colon cancer (version 5.2025 – October 30, 2025) recommend Erbitux as initial therapy for advanced or metastatic *KRAS/NRAS/BRAF* wild-type and left-sided tumors only, in combination with FOLFOX, FOLFIRI, or CapeOX 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. NCCN guidelines recommend Erbitux for advanced or metastatic *KRAS/NRAS/BRAF* wild-type as second-line and subsequent therapy. Erbitux in combination with Braftovi or Braftovi and FOLFOX is recommended for the initial, second-line and subsequent treatment of advanced or metastatic *BRAF V600E* mutation positive disease (category 2A). The NCCN guidelines recommend Erbitux for initial, second-line and subsequent therapy for advanced or metastatic *KRAS G12C* positive tumors, in combination with Lumakras or Krazati (category 2A).
- **Cutaneous Squamous Cell Cancer:** Guidelines (version 1.2026 – September 2, 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]
- **Head and Neck Cancer**: Guidelines (version 5.2025 – August 12, 2025) recommend Erbitux as first-line therapy, in combination with carboplatin for recurrent, unresectable, oligometastatic, or metastatic disease for nasopharyngeal cancers (category 2A). NCCN guidelines also recommend Erbitux as first-line and subsequent therapy for non-nasopharyngeal cancers (category 2A).[4,6]
- **Non-Small Cell Lung Cancer:** Guidelines (version 8.2025 – August 15, 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]
- **Rectal Cancer:** Guidelines for rectal cancer (version 4.2025 – October 31, 2025) recommend Erbitux as initial, second-line, and subsequent therapy for advanced or metastatic *KRAS/NRAS/BRAF* wild-type, in combination with FOLFOX, FOLFIRI, irinotecan, or CapeOX 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] Erbitux in combination with Braftovi is recommended for initial, second-line, and subsequent treatment for advanced or metastatic *BRAF V600E* mutation positive disease (category 2A). The NCCN guidelines recommend Erbituxfor initial, second-line, and subsequent therapy for advanced or metastatic *KRAS G12C* positive tumors, in combination with Lumakras or Krazati (category 2A).
- **Cutaneous Squamous Cell Cancer:** Guidelines (version 1.2026 – September 2, 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

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1. Colon Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
Note: For rectal cancer, refer to the respective criteria under FDA-approved indications.

A) Patient is ≥ 18 years of age; AND

B) Patient has advanced or metastatic disease and meets ONE of the following (i, ii or iii):

i. Patient meets BOTH of the following (a and b):

i. Tumor or metastases are *KRAS*, *NRAS*, and *BRAF* wild-type; AND
Note: The tumor or metastases are *KRAS/NRAS/BRAF* mutation negative.

ii. Patient meets ONE of the following [(1) or (2)]:

1. The primary tumor originated on the left side of the colon; OR
Note: primary tumor originated from the splenic flexure to the rectum.
2. The medication is used as subsequent therapy; OR

ii. Patient meets BOTH of the following (a and b):

(1) Tumor or metastases are *BRAF V600E* mutation-positive; AND

(2) The medication is used in combination with Braftovi (encorafenib capsules); OR

iii. Patient meets BOTH of the following (a and b):

(1) Tumor or metastases are *KRAS G12C* mutation positive; AND

(2) The medication is used in combination with Lumakras (sotorasib tablets) or Krazati (adagrasib tablets); AND

C) The medication 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):

a. Initial Dose: Approve up to 400 mg/m^2 administered by intravenous infusion given once; AND

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b. 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 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 or ii):

i. Patient has non-nasopharyngeal disease; OR

ii. Patient meets BOTH of the following (a and b):

a) Patient has nasopharyngeal disease; AND

b) Patient has recurrent, unresectable, oligometastatic, or metastatic disease; AND

C) The medication 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):

a. Initial Dose: Approve up to 400 mg/m^2 administered by intravenous infusion, give once; AND

b. 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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3. Rectal Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

Note: For colon cancer, refer to the respective criteria under FDA-approved indications.

A) Patient is ≥ 18 years of age; AND

B) Patient has advanced or metastatic disease and meets ONE of the following (i, ii, or iii):

i. Tumor or metastases are *KRAS*, *NRAS*, and *BRAF* wild-type; OR
Note: The tumor or metastases are *KRAS/NRAS/BRAF* mutation negative.

ii. Patient meets BOTH of the following (a and b):

a) Tumor or metastases are *BRAF V600E* mutation-positive; AND

b) The medication is used in combination with Braftovi (encorafenib capsules); OR

iii. Patient meets BOTH of the following (a and b):

a) Tumor or metastases are *KRAS G12C* mutation positive; AND

b) The medication is used in combination with Lumakras (sotorasib tablets) or Krazati (adagrasib tablets); AND

C) The medication 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.

Other Uses with Supportive Evidence

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4. 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, ii or iii):

i. Patient meets BOTH of the following (a and b):

(1) Tumor or metastases are *KRAS/NRAS/BRAF* wild-type; AND
Note: The tumor or metastases are *KRAS*, *NRAS*, and *BRAF* mutation negative

b) The medication is used for subsequent therapy; OR

ii. Patient meets BOTH of the following (a and b):

a) Tumor or metastases are *BRAF V600E* mutation-positive; AND

b) The medication is used in combination with Braftovi (encorafenib capsules); OR

iii. Patient meets ALL of the following (a, b, and c):

a) Tumor or metastases are *KRAS G12C* mutation positive; AND

b) The medication is used for subsequent therapy; AND

c) The medication is used in combination with Lumakras (sotorasib tablets) or Krazati (adagrasib tablets); AND

C) The medication 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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5. Cutaneous Squamous Cell 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 has locally advanced, recurrent, or metastatic disease; AND

C) The medication 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.

6. 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) The medication will be used in combination with Gilotrif (afatinib tablets); AND

F) The medication 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.

7. Penile Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):

A) Patient is ≥ 18 years of age; AND

B) Patient has recurrent or metastatic disease; AND

C) The medication will be used as subsequent therapy; AND

D) The medication 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.
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3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 4.2025 – October 31, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 10, 2025.
4. The NCCN Head and Neck Cancer Clinical Practice Guidelines in Oncology (version 5.2025 – August 12, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 10, 2025.
5. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2026 – November 6, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 10, 2025.
6. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 10, 2025. Search term: cetuximab.
7. The NCCN Penile Cancer Clinical Practice Guidelines in Oncology (version 2.2025 – January 6, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 10, 2025.
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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.
14. The NCCN Appendiceal Neoplasms and Cancer Clinical Practice Guidelines in Oncology (version 1.2026 – October 30, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 31, 2025.

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. **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	08/02/2023

	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.	
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. **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). **Appendiceal Adenocarcinoma:** Added new condition of approval. **Penile Cancer:** Added recurrent to requirement that the patient has recurrent or metastatic disease.	08/07/2024
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/16/2024
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 as a Note. Added metachronous metastases are metastases that are diagnosed months to years after the initial diagnosis of colon or rectal cancer. **Appendiceal Adenocarcinoma:** Medication is used for subsequent treatment removed as a requirement.	02/26/2025
Aspirus P&T Review	Policy reviewed and approved by Aspirus P&T committee. Annual review process	09/15/2025
Early Annual Revision	**Colon Cancer**: This indication was changed to as listed (previously was Colon and Rectal Cancer). A note was added stating: "For rectal cancer, refer to the respective criteria under FDA-approved indications". The following options of approval along with their associated notes were removed: The patient has unresectable synchronous liver and/or lung metastases; patient has unresectable metachronous metastases. For a patient with advanced or metastatic disease, the following requirements were removed: The medication is used for initial treatment; the medication is used as a single agent or in combination with irinotecan, FOLFOX, CapeOX, or FOLFIRI. In the option of approval that the tumor or metastases are *KRAS G12C* mutation positive, the requirement that the medication is used for subsequent therapy was removed. **Head and Neck Cancer:** This indication was changed to as listed (previously was head and neck squamous cell carcinoma). The options of approval that the medication will be used as a single agent or in combination with radiation therapy, platinum-based therapy, paclitaxel or docetaxel, Keytruda (pembrolizumab intravenous infusion) or Opdivo (nivolumab intravenous infusion) were removed. Options for approval were added for non-nasopharyngeal disease and	11/19/2025

	nasopharyngeal disease with recurrent, unresectable, oligometastatic, or metastatic disease. **Rectal Cancer:** This new condition of approval was added. **Appendiceal Adenocarcinoma:** Options for approval were added to include cases where tumor or metastases are *KRAS/NRAS/BRAF* wild-type and the medication is used for subsequent therapy. **Penile Cancer:** The requirement that Erbitux will be used as a single agent was removed. **Cutaneous Squamous Cell Cancer**: This indication was changed to as listed (previously was Squamous Cell Skin Cancer). The following options of approval were removed: The patient has locally advanced, high-risk, or very high-risk disease; patient has unresectable, inoperable, or incompletely resected regional disease; patient has local or regional recurrence; and patient has distant metastases. The requirement that patient has locally advanced, recurrent, or metastatic disease was added.	