Clinical Policy: Cetuximab (Erbitux)

Reference Number: ERX.SPA.261
Effective Date: 12.01.18
Last Review Date: 11.20
Line of Business: Commercial, Medicaid

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 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) with 5-FU;*
   **Prior authorization may be required for platinum-based therapies and 5-FU.*
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 or b):
   a. Wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS*);
   b. BRAF wild-type;
5. One of the following (a, b, c, d, or e):*
   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 or without oxaliplatin- or irinotecan-based chemotherapy (e.g., FOLFOXIRI), without irinotecan or oxaliplatin followed by FOLFOX, or member is intolerant to irinotecan or oxaliplatin: Prescribed in combination with Braftovi® if BRAF V600E mutation positive (off-label);
   d. Previous treatment with an oxaliplatin containing regimen (e.g., FOLFOX, CapeOx): Prescribed in combination with FOLFIRI, Braftovi®, or irinotecan**,** if BRAF V600E mutation positive (off-label);
   e. Previous treatment with FOLFIRI: Prescribed in combination with irinotecan if BRAF V600E mutation positive (off-label);

   **Prior authorization may be required*
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

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®, Iressa®);*

   **Prior authorization may be required for EGFR TKI therapies*
6. Prescribed in combination with Gilotrif as subsequent therapy;*

   **Prior authorization may be required for Gilotrif*
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. 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 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 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
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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 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. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
Modified FOLFOX 6	**CRC** Day 1: oxaliplatin 85 mg/m^2 IV Day 1: Folinic acid 400 mg/m^2 IV 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 Repeat cycle every 2 weeks.	See dosing regimen
CapeOX	**CRC** Day 1: Oxaliplatin 130 mg/m^2 IV Days 1–14: Capecitabine 1,000 mg/m^2 PO BID Repeat cycle every 3 weeks.	See dosing regimen
FOLFIRI	**CRC** Day 1: Irinotecan 180 mg/m^2 IV Day 1: Leucovorin 400 mg/m^2 IV Day 1: Flurouracil 400 mg/m^2 IV followed by 2,400 mg/m^2 continuous IV over 46 hours Repeat cycle every 14 days.	See dosing regimen
FOLFOXIRI	**CRC** 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) Repeat cycle every 2 weeks.	See dosing regimen
Gilotrif (afatinib)	**Metastatic NSCLC** 40 mg PO QD	40 mg/day; 50 mg/day when on chronic concomitant therapy with a P-gp inducer
Iressa (gefitinib)	**Metastatic NSCLC** 250 mg PO QD	250 mg/day; 500 mg/day when used with a strong CYP3A4 inducer
Tarceva (erlotinib)	**Metastatic NSCLC** 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** 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 Repeat every 3 to 4 weeks.	See dosing regimen
5-FU, cisplatin	**HNSCC** cisplatin 100 mg/m2 IV or carboplatin AUC 5 IV on day 1, plus 5-FU 1,000 mg/m2 IV on days 1, 2, 3, and 4, repeated every 3 weeks **Penile Cancer** 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	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
	Repeat every 3 to 4 weeks.	
Braftovi (encorafenib)	**CRC** 300 mg PO once daily in combination with cetuximab (400 mg/m2 IV over 120 minutes on day 1 followed by weekly infusions of cetuximab 250 mg/m2 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.*

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
HNSCC, CRC	Weekly schedule: initial dose: 400 mg/m^2 IV followed by 250 mg/m^2 IV weekly 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; April 2021. Available at: http://uspl.lilly.com/erbitux/erbitux.html. Accessed May 26, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 17, 2020.
3. National Comprehensive Cancer Network. Colon Cancer Version 4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 17, 2020.
4. National Comprehensive Cancer Network. Rectal Cancer Version 6.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed August 17, 2020.
5. National Comprehensive Cancer Network. Head and Neck Cancer Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed August 17, 2020.
6. National Comprehensive Cancer Network. Penile Cancer 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/penile.pdf. Accessed August 17, 2020.
7. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer 6.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 17, 2020.
8. National Comprehensive Cancer Network. Squamous Cell Skin Cancer 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed August 17, 2020.

9. Cosyntropin Drug Monograph. Clinical Pharmacology. Tampa, FL: Gold Standard Inc.; 2020. Available at: http://www.clinicalpharmacology-ip.com. Accessed August 17, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	08.07.18	11.18
4Q 2019 annual review: no significant changes; references reviewed and updated.	08.13.19	11.19
4Q 2020 annual review: added criteria to HNSCC indication for use as single agent or in combination with platinum based therapy with 5-FU; added BRAF disease wild-type and for treatment in combination with Braftovi if BRAF V600E mutation position to colorectal indication as per NCCN 2A or above off label indication; references reviewed and updated.	08.17.20	11.20
Updated HNSCC and CRC dosing to include biweekly dosing option per updated prescribing information.	05.26.21	

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.