Clinical Policy: Cetuximab (Erbitux)

Reference Number: CP.PHAR.317
Effective Date: 02.01.17
Last Review Date: 11.20
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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.

It is the policy of health plans affiliated with Centene Corporation® 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 or b):*
   a. Dose does not exceed an initial dose of 400 mg/m^2 followed by 250 mg/m^2 weekly thereafter;
   b. 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 or b):*
   a. Dose does not exceed an initial dose of 400 mg/m^2 followed by 250 mg/m^2 weekly thereafter;
   b. 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®, or 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, CP.PMN.53 for Medicaid, and HIM-Medical Benefit.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene 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 HNSCC or CRC: new dose does not exceed 250 mg/m^2 weekly;

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 Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid 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 for all relevant lines of business 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	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Repeat cycle every 2 weeks.	
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, carboplatin	**HNSCC** 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 **Penile Cancer**	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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 Repeat every 3 to 4 weeks.	
Braftovi (encorafenib)	**CRC** 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.*

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
HNSCC, CRC	Initial dose: 400 mg/m^2 IV followed by 250 mg/m^2 IV weekly	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 2019. Available at: http://uspl.lilly.com/erbitux/erbitux.html. Accessed August 17, 2020.
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.

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.

HCPCS Codes	Description
J9055	Injection, cetuximab, 10 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from CP.PHAR.182 Excellus Oncology. NCCN off-label recommended uses added. HNSCC subtypes by location outlined at Appendix B. CRC: EGFR testing is removed from the FDA labeled criteria. NRAS wild type (i.e., not mutated) is added to KRAS wild type. Some NCCN colon cancer off-label recommendations are collapsed and combined into a colorectal section with some rectal cancer indications.	01.17	02.17
Policy converted to new template. Annual Review. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs. Criteria with NCCN 2B rating recommendations removed. Added criteria for NCCN 2A or above off-label indications for NSCLC, penile cancer, and squamous cell skin cancer. Authorization limits extended from 3 and 6 months to 6 and 12 months for initial and continued approval, respectively.	08.30.17	11.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2018 annual review: no significant changes; added Commercial and HIM lines of business; summarized NCCN and FDA-approved uses for improved clarity; added specialist involvement in care; references reviewed and updated.	07.25.18	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

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

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

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.