

Clinical Policy: Cetuximab (Erbix)

Reference Number: PA.CP.PHAR.317

Effective Date: 01/2018

Last Review Date: 10/2024

Description

Cetuximab (Erbix[®]) is an epidermal growth factor receptor (EGFR) antagonist.

FDA Approved Indication(s)

Erbix is indicated for treatment of:

- Head and neck squamous cell carcinoma (HNSCC)
 - Locally or regionally advanced HNSCC in combination with radiation therapy for initial treatment
 - Recurrent locoregional disease or metastatic HNSCC in combination with platinum-based therapy with fluorouracil (5-FU) for first-line treatment
 - Recurrent or metastatic HNSCC progressing after platinum-based therapy, as a single agent
- Colorectal cancer (CRC)
 - *K-Ras* wild-type, EGFR-expressing, metastatic CRC as determined by an FDA-approved test
 - In combination with FOLFIRI (irinotecan, fluorouracil, 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
 - BRAF V600E mutation-positive metastatic CRC
 - In combination with encorafenib, for the treatment of adult patients with metastatic CRC with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy

Limitation(s) of use: Erbix is not indicated for treatment of *Ras*-mutant CRC or when the results of the *Ras* mutation tests are unknown.

Policy/Criteria

It is the policy of PA Health & Wellness[®] that Erbix 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 \geq 18 years;
4. Disease is advanced, recurrent, unresectable, or metastatic;
5. Prescribed in one of the following (a or b)
 - a. As a single agent;

- b. In combination with platinum-based therapy (e.g., cisplatin or carboplatin), Opdivo[®], Keytruda[®], paclitaxel, or docetaxel (if cisplatin-ineligible);*;
**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/m² followed by 250 mg/m² weekly thereafter;
 - b. Dose does not exceed 500 mg/m² 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*).

Approval duration: 6 months

B. Colorectal Cancer (must meet all):

1. Diagnosis of advanced, unresectable, or metastatic colorectal cancer (CRC);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is one of the following (a, b, c, d or e)
 - a. KRAS/NRAS/BRAF wild-type (i.e., no mutations in KRAS, NRAS, or BRAF genes);
 - b. BRAF V600E mutation positive;
 - c. KRAS G12C mutation positive;
 - d. Deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H);
 - e. Polymerase epsilon/delta (POLE/POLD1) mutation positive;
5. Prescribed in one of the following ways (a, b, c, d or e):*
 - a. As a single agent;
 - b. In combination with FOLFIRI, FOLFOX, CapeOX;
 - c. In combination with irinotecan in the initial or subsequent line setting;
 - d. IF BRAF V600E mutation positive: In combination with Braftovi[®] if following prior therapy;
 - e. If KRAS G12C mutation positive: In combination with Lumakras or Krazati if following prior therapy;**Prior authorization may be required*
6. For colon cancer that is KRAS/NRAS/BRAF wild-type with unresectable synchronous liver and/or lung metastases: colon cancer is left-sided only (*see Appendix E*);
7. For dMMR/MSI-H or POLE/POLD1 mutation positive cancer: Member is ineligible for or has progressed on checkpoint inhibitor immunotherapy (*see Appendix B*);
8. Request meets one of the following (a, b, or c):*
 - a. Dose does not exceed an initial dose of 400 mg/m² followed by 250 mg/m² weekly thereafter;
 - b. Dose does not exceed 500 mg/m² 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*).

Approval duration: 6 months

C. Non-Small Cell Lung Cancer (off-label) (must meet all):

1. Diagnosis of recurrent, advanced, or metastatic non-small cell lung cancer;
2. Prescribed by or in consultation with an oncologist;

3. Age \geq 18 years;
4. Tumor is EGFR exon 19 deletion or exon 21 L858R, EGFR S768I, L861Q, and/or G719X mutation positive;
5. Prescribed in combination with Gilotrif as subsequent therapy;
**Prior authorization is may be required for Gilotrif*
6. One of the following (a or b):
 - a. Disease has progressed on or after an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., Tarceva[®], Gilotrif[®], or Iressa[®]);*
 - b. Tumor is T790M positive and disease has progressed on or after Tagrisso[®];
**Prior authorization may be required for Tagrisso and EGFR TKI therapies*
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*).

Approval duration: 6 months

D. Penile Cancer (off-label) (must meet all):

1. Diagnosis of metastatic or recurrent penile cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Prescribed as a single agent;
5. Prescribed as subsequent-line systemic therapy;
6. 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*).

Approval duration: 6 months

E. Squamous Cell Skin Cancer (off-label) (must meet all):

1. Diagnosis of squamous cell skin cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
 - a. Prescribed in one of the following ways (a or b):As a single agent;
 - b. If member is ineligible for or progressed on immune checkpoint inhibitors (*see Appendix B*) and clinical trials: combination with carboplatin and paclitaxel;
4. Disease is advanced, unresectable, high-risk, recurrent, metastatic, inoperable or not fully resectable;
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*).

Approval duration: 6 months

F. Other diagnoses/indications: Refer to PA.CP.PMN.53.

II. Continued Approval

A. All Indications in Section I (must meet all):

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met initial approval criteria, or the Continuity of Care policy applies (*see PA.PHARM.01*);
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/m² weekly or 500 mg/m² 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*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy, or the Continuity of Care policy applies (*see PA.PHARM.01*); or
2. Refer to PA.CP.PMN.53

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 – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

5-FU: fluorouracil	FOLFOXIRI: fluorouracil, leucovorin, oxaliplatin, irinotecan
CapeOX: capecitabine, oxaliplatin	HER: human epidermal growth factor receptor
CRC: colorectal cancer	HNSCC: head and neck squamous cell carcinoma
dMMR/MSI-H: deficient mismatch repair/microsatellite instability-high	KRAS: Kirsten rat sarcoma 2 viral oncogene homologue
EGFR: epidermal growth factor receptor	NRAS: neuroblastoma RAS viral oncogene homologue
FDA: Food and Drug Administration	
FOLFIRI: fluorouracil, leucovorin, irinotecan	
FOLFOX: fluorouracil, leucovorin, oxaliplatin	POLE/POLD1: polymerase epsilon/delta

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	See dosing regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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.	
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
Checkpoint inhibitor therapies: Opdivo [®] (nivolumab) ± Yervoy [®] (ipilimumab) or Keytruda [®] (pembrolizumab)	CRC Varies	Varies
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
Tagrisso [®] (osimertinib)	NSCLC 80 mg PO QD	80 mg/day; 160 mg/day when used with a strong CYP3A inducer

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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/m ² 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 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.	See dosing regimen
Immune checkpoint inhibitors: Keytruda (pembrolizumab), Libtayo [®] (cemiplimab-rwlc)	Squamous Cell Skin Cancer Varies	Varies

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.*

Appendix E: KRAS/NRAS/BRAF Wild-Type Colon Cancer with Unresectable, Synchronous Liver and/or Lung Metastases

- The NCCN Colon Cancer Guidelines recommend that cetuximab should only be used for left-sided tumors in KRAS/NRAS/BRAF wild-type colon cancer with unresectable, synchronous liver and/or lung metastases. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab. Data on the response to cetuximab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.

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; September 2021. Available at: <https://erbitux.lilly.com/hcp>. Accessed July 17, 2024.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 7, 2024.
3. National Comprehensive Cancer Network. Head and Neck Cancer Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed August 8, 2024.
4. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer 7.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 8, 2024.
5. National Comprehensive Cancer Network. Squamous Cell Skin Cancer 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed August 8, 2024.
6. National Comprehensive Cancer Network. Colon Cancer 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 8, 2024.

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
4Q 2018 annual review: no significant changes; summarized NCCN and FDA-approved uses for improved clarity; added specialist involvement in care; references reviewed and updated	07/2018
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/2019
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.	10/2020
4Q 2021 annual review: for CRC simplified requirements for prior and combination therapy; updated place in therapy for penile and squamous cell skin cancer per NCCN Compendium; for brand name requests added requirement for trial of generic equivalent if available; references reviewed and updated.	10/2021
4Q 2022 annual review: for HNSCC, removed required 5-FU combination per NCCN; added “advanced, unresectable, or metastatic” for CRC setting and “after prior therapy” if BRAF V600E positive for CRC per NCCN; for NSCLC, removed requirement that tumor be T790M negative and added T790M positive option per NCCN; for skin cancer, added criterion that for use as a single agent and removed basal cell carcinoma indication per NCCN; removed template generic redirection language as this an injectable agent; references reviewed and updated.	10/2022
4Q 2023 annual review: for HNSCC added combination therapy with Opdivo per NCCN; for CRC added CapeOX as a possible combination therapy per NCCN; for colon cancer that is KRAS/NRAS/BRAF wild-type added criterion that disease is left-sided only per NCCN, along with rationale in Appendix E; for squamous cell skin cancer, removed “locally” from locally advanced disease qualifier as disease can be regional per NCCN; references reviewed and updated.	10/2023
4Q 2024 annual review: per NCCN – for HNSCC, added qualifier of unresectable disease and added alternative combinations with Keytruda, paclitaxel, or docetaxel; for CRC, dMMR/MSI-H, and POLE/POLD1 mutations with corresponding requirements related to combination use and/or prior therapy, and modified requirement for left-sided colon cancer to only apply to unresectable synchronous liver/lung metastases; for NSCLC, specified sensitizing EGFR mutations (EGFR exon 19 deletion or exon 21 L858R, EGFR S768I, L861Q, and/or G719X mutation positive); for penile	10/2024

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Reviews, Revisions, and Approvals	Date
cancer, added qualifier of recurrent disease; for squamous cell skin cancer, added qualifiers of unresectable and recurrent disease, removed qualifier of very high risk, and added pathway for combination use with carboplatin and paclitaxel; references reviewed and updated.	