Clinical Policy Title:	cetuximab
Policy Number:	RxA.266
Drug(s) Applied:	Erbitux®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2021
Line of Business Policy Applies to:	All line of business

Background

Cetuximab (Erbitux®) is an epidermal growth factor receptor (EGFR) antagonist, 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.
  - BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC):
    - In combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
cetuximab (Erbitux®)	HNSCC, CRC	Premedicate with an H_1 receptor antagonist. <u>In combination with radiation therapy:</u> Initial dose: 400 mg/m^2 administered as a 120-minute intravenous infusion one week prior to initiating a course of radiation therapy. Subsequent doses: 250 mg/m^2 administered as a 60-minute infusion every week for the duration of radiation therapy (6–7 weeks). Complete Erbitux® administration 1 hour prior to radiation therapy.	400 mg/ m^2 intravenously for the initial dose then 250 mg/ m^2 intravenously once weekly for subsequent doses; or 500 mg/ m^2 intravenously every 2 weeks.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
		As a single-agent or in combination with chemotherapy weekly: Administer initial dose of 400 mg/m^2 as a 120-minute intravenous infusion, and subsequent doses of 250 mg/m^2 infused over 60 minutes once weekly. Biweekly: Administer 500 mg/m^2 as 120-minute intravenous infusion every two weeks. Complete Erbitux® administration 1 hour prior to chemotherapy. Continue treatment until disease progression or unacceptable toxicity. In combination with encorafenib (for CRC only). The recommended initial dose is 400 mg/m^2 administered as a 120-minute intravenous infusion in combination with encorafenib. The recommended subsequent dosage is 250 mg/m^2 weekly as a 60-minute infusion in combination with encorafenib until disease progression or unacceptable toxicity.	

Dosage Forms

- Single-dose vials: 100 mg/50 mL, 200 mg/100 mL.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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. 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; or 500 mg/ m^2 intravenously every 2 weeks 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
Commercial: 6 months
Medicaid: 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. Request meets one of the following (a or b):
   a. Disease is KRAS or NRAS wild-type (i.e., not mutated);
   b. Disease is positive for BRAF V600E mutation and prescribed in combination with encorafenib;
5. For KRAS or NRAS wild- type only, one of the following (a or b):
   a. Request is for first-line treatment: Prescribed in combination with FOLFOX or FOLFIRI;
   b. Previous treatment with oxaliplatin- and irinotecan-based chemotherapy (e.g., FOLFOXIRI) or member is intolerant to irinotecan;
   c. Previous treatment with an oxaliplatin containing regimen (e.g., FOLFOX, CapeOx): Prescribed in combination with FOLFIRI, irinotecan;
   d. Previous treatment with FOLFIRI: Prescribed in combination with irinotecan;
6. For BRAF V600F mutation positive disease used in combination with encorafenib, one of the following (a or b);
   a. Used as subsequent therapy for disease progression after at least one prior line of treatment in the advanced or metastatic disease setting;
   b. Used as primary treatment for unresectable metastatic disease after previous adjuvant FOLFOX or CapeOX within the past 12 months;
7. 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; or 500 mg/ m^2 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
Commercial: 6 months
Medicaid: 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 ≥ 18 years;
4. Is used in combination with Gilotrif® as subsequent therapy for EGFR mutation positive for and meet one of following (a or b or c):
   a. Is T790M negative, have progressed on EGFR tyrosine kinase inhibitor therapy (e.g Tarceva®, Gilotrif®, or Iressa®);
   b. Is T790M positive, have progressed on osimertinib;
   c. Who have progressed on EGFR tyrosine kinase inhibitor therapy for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited 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
Commercial: 6 months

Medicaid: 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. Member has received prior systemic chemotherapy (e.g., paclitaxel, ifosfamide, cisplatin, 5-FU);
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
Commercial: 6 months
Medicaid: 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**
1. Member is currently receiving medication that has been authorized by RxAdvance 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;
   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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Modified Folfox 6	**CRC** Day 1: oxaliplatin 85 mg/m^2 intravenously Day 1: folinic acid 400 mg/m^2 intravenously Days 1-3: 5-FU 400 mg/m^2 intravenous bolus on day 1, then 1,200 mg/m^2/day × 2 days (total 2,400 mg/m^2 over 46–48 hours) intravenous continuous infusion, repeat cycle every 2 weeks.	See dosing regimen
CapeOX	**CRC** Day 1: oxaliplatin 130 mg/m^2 intravenously Days 1–14: capecitabine 1,000 mg/m^2 orally twice daily repeat cycle every 3 weeks.	See dosing regimen
Folfiri	**CRC** Day 1: Irinotecan 180 mg/m^2 intravenously Day 1: Leucovorin 400 mg/m^2 intravenously Day 1: Fluorouracil 400 mg/m^2 intravenously followed by 2,400 mg/m^2 continuous intravenously over 46 hours repeat cycle every 14 days.	See dosing regimen
Folfoxiri	**CRC** Day 1: Irinotecan 165 mg/m^2 intravenously, oxaliplatin 85 mg/m^2 intravenously, leucovorin 400 mg/m^2 intravenously, fluorouracil 1,600 mg/m^2 continuous intravenously for 2 days (total 3,200 mg/m^2) repeat cycle every 2 weeks.	See dosing regimen
Gilotrif®	**Metastatic NSCLC** 40 mg orally once daily	40 mg/day; 50 mg/day when on chronic concomitant therapy with a P-gp inducer

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Iressa®	**Metastatic NSCLC** 250 mg orally once daily	250 mg/day; 500 mg/day when used with a strong CYP3A4 inducer
erlotinib (Tarceva®)	**Metastatic NSCLC** 150 mg orally once daily	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** Day 1: Paclitaxel 175 mg/m^2 intravenously Days 1-3: ifosfamide 1,200 mg/m^2 intravenously, cisplatin 25 mg/m^2 intravenously repeat every 3 to 4 weeks.	See dosing regimen
5-FU, cisplatin	**Penile Cancer** Day 1: cisplatin 70-80 mg/m^2 intravenously Days 1-4 or 2-5: 5-FU 800 - 1,000 mg/m^2/day continuous intravenously repeat every 3 to 4 weeks.	See dosing regimen

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - Infusion reactions and cardiopulmonary arrest.

APPENDIX D: General Information

- 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.

References

1. Erbitux® Prescribing Information. Indianapolis, IN: Eli Lilly and Company; September 2021. Available at: http://uspl.lilly.com/erbitux/erbitux.html. Accessed October 28, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at:

http://www.nccn.org/professionals/drug_compendium. Accessed October 28, 2021.
3. Clinical Pharmacology powered by ClinicalKey. Tampa, FL: Elsevier, 2021. Available at: http://www.clinicalkey.com. Accessed October 28, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical policy title updated. 2. Line of Business Policy Applies to was updated to all lines of business. 3. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance... 4. Reference reviewed and updated	08/25/2020	09/14/2020
Policy was reviewed: 1. Dosing Information dosing regimen was updated to include “Premedicate with an H1 receptor antagonist…” and “Complete Erbitux® administration 1 hour prior to radiation therapy…”. 2. Dosing Information maximum dose was updated to include “400 mg/ m^2 intravenously for the initial dose…”. 3. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 4. Initial Approval Criteria I.A.5.a was updated to include “or 500 mg/ m^2 intravenously every 2 weeks”. 5. Initial Approval Criteria I.B.5.c and d were updated to remove “irinotecan with Zelboraf® if BRAF V600E mutation positive”. 6. Initial Approval Criteria I.B.6 was updated to include “Subsequent therapy in combination with encorafenib…”. 7. Initial Approval Criteria I.B.7 was updated to include “Primary treatment for patients with unresectable metachronous metastases…”. 8. Initial Approval Criteria I.B.8.a was updated to include “OR 500 mg/ m^{2}”. 9. Continued Therapy Approval Criteria	05/31/2021	09/14/2021

II.A.3.a was updated to include “or 500 mg/ m^2”. 10. Appendix B footnote was updated to,” Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only. 11. References were reviewed and updated.		
Policy was reviewed: 1. Background was updated to include new indication “BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)”. 2. Dosing information was updated to include “In combination with encorafenib”. 3. Initial approval criteria I.B.4.b was updated to include “Disease is positive for BRAF V600E mutation and prescribed in combination with encorafenib”. 4. Initial approval criteria I.B.6 was added. 5. Initial approval criteria I.C.1 was updated to include “recurrent, advanced, or metastatic disease”. 6. Initial approval criteria I.C.4.a, b,c were added per NCCN guidelines . 7. Initial approval criteria I.C.5 “Disease has progressed on or after an EGFR tyrosine kinase inhibitor” was removed. 8. Initial approval criteria I.C.6 “Prescribed in combination with Gilotrif® as subsequent therapy” was removed. 9. Continued Therapy Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 10. References were reviewed and updated.	10/28/2021	12/07/2021