Clinical Policy: Cetuximab (Erbitux)

Reference Number: PA.CP.PHAR.317
Effective Date: 01/18
Last Review Date: 11/17

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness ® clinical policy for cetuximab for injection (Erbitux®).

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness ® 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 head and neck squamous cell carcinoma (HNSCC) (see Appendix B for subtypes by location);
2. Meets a or b:
   a. FDA-approved use (must meet one):
      i. Locally or regionally advanced disease (Stage III/IV) in combination with radiation therapy;
      ii. Recurrent locoregional or metastatic disease in combination with platinum-based therapy with 5-FU;
      iii. Recurrent or metastatic disease progressing after platinum-based therapy;
   b. Off-label NCCN recommended use:
      i. For recurrent/persistent, unresectable or metastatic disease (a, b, or c):
         a) In combination with carboplatin;
         b) As a single agent or in combination with either a) cisplatin or b) fluorouracil (with cisplatin or carboplatin) for any HNSCC subtype except nasopharyngeal cancer (see Appendix B for subtypes by location);
         c) In combination with docetaxel or paclitaxel for metastatic non-nasopharyngeal cancer.

Approval duration: 3 months

B. Colorectal Cancer (must meet all):

1. Diagnosis of colorectal cancer (CRC);
2. Disease is KRAS or NRAS wild type (i.e., not mutated);
3. Meets a or b:
   a. FDA approved use:
      i. Prescribed for metastatic CRC (a, b, or c):
         a) As primary therapy in combination with FOLFIRI*;
         b) As subsequent therapy in combination with irinotecan if refractory to irinotecan-based chemotherapy;
         c) As subsequent therapy as a single agent (1 or 2):
            1) After failing oxaliplatin- and irinotecan-based chemotherapy;
            2) If intolerant to irinotecan;

b. Off-label NCCN recommended use:
   i. Prescribed for unresectable, metastatic or inoperable CRC (a, b or c):
      a) As primary therapy;
      b) As subsequent therapy (1, 2 or 3):
         1) If not previously treated with cetuximab or panitumumab;
         2) Following primary treatment with chemoradiation or local therapy;
         3) For unresectable advanced or metastatic disease;
      c) As adjuvant therapy** (1 or 2):
         1) For unresectable metastatic disease that has converted to resectable disease;
         2) Following resection and/or local therapy for metastases if (i or ii):
            i) Member has received previous chemotherapy;
            ii) Positive for growth on neoadjuvant** chemotherapy;
   ii. Prescribed for rectal cancer in combination with FOLFO* or FOLFIRI*, or as a single agent if intensive therapy is not appropriate:
      a) As primary therapy for disease characterized as (one of the following):
         1) T3, N0, M0 (Stage IIA)†;
         2) Any T, N1-2, M0 (Stage III)†;
         3) T4 (Stage IIB-C, Stage IIIB-C, Stage IV)†;
         4) Locally unresectable or inoperable disease with no metastases if resection is contraindicated following neoadjuvant** therapy.

**FOLFIRI (fluorouracil, leucovorin, irinotecan); FOLFOX (fluorouracil, leucovorin, oxaliplatin).*
***Adjuvant therapy (therapy administered after the main treatment to help decrease the risk of cancer recurring); neoadjuvant therapy (therapy given as a first step to shrink a tumor before the main therapy).*
†T (primary tumor characteristics); N (regional lymph nodes); M (metastatic disease).

Approval duration: 3 months

C. Other diagnoses/indications: Refer to PA.CP.PMN.53.
1. The following NCCN recommended uses for Erbitux, meeting NCCN categories 1 or 2a are approved per CP.PMN.53:
   a. Squamous cell skin cancer;
   b. Non-small cell lung cancer (NSCLC);
   c. Penile cancer.

II. Continued Approval

A. All Indications (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met initial approval criteria, or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*);
2. Member has none of the following reasons to discontinue:
   a. Disease progression or unacceptable toxicity;
   b. Serious infusion reactions requiring medical intervention and/or hospitalization;
   c. Severe acneiform rash:
      i. Recurrence that does not improve after a one-to-two week infusion delay;

ii. Fourth recurrence;
d. Interstitial lung disease.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy, or the Continuity of Care policy applies (*see PA.LTSS.PHAR.01*); or
2. Refer to PA.CP.PMN.53 - Global Biopharm Policy**.**

Background
Description/Mechanism of Action:
The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. In vitro assays and in vivo animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Signal transduction through the EGFR results in activation of wild-type Ras proteins, but in cells with activating Ras somatic mutations, the resulting mutant Ras proteins are continuously active regardless of EGFR regulation.

In vitro, cetuximab can mediate antibody-dependent cellular cytotoxicity) against certain human tumor types. In vitro assays and in vivo animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

Formulations:
Erbitux (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid containing no preservatives.
- 100 mg/50 mL, single-use vial, individually packaged in a carton
- 200 mg/100 mL, single-use vial, individually packaged in a carton

FDA Approved Indications:

Erbitux is an epidermal growth factor receptor (EGFR) antagonist/intravenous formulation indicated for:

- Head and Neck Cancer
  - 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 5-FU.
  - Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.
- Colorectal Cancer
  - K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests:
    - 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 of use: Erbitux is not indicated for treatment of RAS-mutant colorectal cancer.

Appendices

Appendix A: Abbreviation Key

5-FU: Fluorouracil
EGF: Epidermal growth factor
EGFR: Epidermal growth factor receptor
FOLFIRI: Fluorouracil, leucovorin, irinotecan
FOLFOX: Fluorouracil, leucovorin, oxaliplatin
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
NSCLC: Non-small cell lung cancer

Appendix B: Head and Neck Squamous Cell Cancers by Location*[5]

- Paranasal sinuses (ethmoid, maxillary)
- Larynx (glottis, supraglottis)
- Pharynx (nasopharynx, oropharynx, hypopharynx)
- Lip and oral cavity
- Major salivary glands (parotid, submandibular, sublingual)
- Occult primary

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**Squamous cell carcinoma, or a variant, is the histologic type in more than 90% of head and neck cancers.*

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	Approval Date

References

1. Erbitux prescribing information. Indianapolis, IN: Eli Lilly and Company; October 2016. Available at http://uspl.lilly.com/erbitux/erbitux.html. Accessed January 24, 2017.
2. Cetuximab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 24, 2017.
3. Head and neck cancers (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 24, 2017.
4. Colon cancer (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 24, 2017.
5. Rectal cancer (Version 2.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 24, 2017.