Cetuximab (Erbitux®)

NDC CODE(S) 66733-0948-XX ERBITUX 100MG/50ML Solution (ELI LILLY & CO.)
66733-0958-XX ERBITUX 2MG/ML Solution (ELI LILLY & CO.)

DESCRIPTION

Cetuximab is a recombinant human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). EGFR is a transmembrane glycoprotein expressed in multiple normal epithelial tissues and in many human cancers. By binding to the EGFR, cetuximab competitively inhibits the binding of natural ligands, including epidermal growth factor (EGF). This blocks the complex downstream signaling of the EGFR cascade and results in inhibition of cell growth, induction of apoptosis and decreased production of matrix metalloproteinase and vascular endothelial growth factor (VEGF).

In the EGFR cascade, RAS proteins, including KRAS, normally function as switches in the kinase pathway activated between cell surface EGFR and downstream signaling. Mutations in the KRAS gene, occurring in 30% to 50% of colorectal cancers and common in other tumor types, activate the EGFR pathway and bypass the need for ligand binding. This renders cetuximab and other anti-EGFR agents ineffective against those tumors expressing RAS mutations such as KRAS and, found more recently, those in another of the RAS proteins, NRAS.

Another common mutation is found in the BRAF gene, a serine/threonine kinase. BRAF encodes a component downstream of the RAS proteins in the EGFR cascade. The BRAF gene is important for transducing mitogenic signals from the cell surface. BRAF mutations have been found in thyroid, colorectal and lung cancers as well as in a majority of malignant melanomas.

POLICY

- Cetuximab for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Colorectal Cancer
  - Head and Neck Cancer (Squamous Cell)
  - Non-Small Cell Lung Cancer
  - Penile Cancer
  - Skin Cancer (Squamous Cell)
- Cetuximab for the treatment of other conditions/diseases is considered ***investigational.***
- Testing for mutation of the *BRAF* gene in the use of cetuximab is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

- Patient is at least 18 years of age**; AND**

Colorectal Cancer (CRC)

- Patient is both KRAS and NRAS mutation negative (wild-type) as determined by an FDA-approved or CLIA-compliant test*; **AND**
- Will not be used as part of an adjuvant treatment regimen; **AND**
- Patient has not been previously treated with cetuximab or panitumumab; **AND**
  - Patient has metastatic, unresectable, or advanced disease that is BRAF mutation negative (wild-type); **AND**

- Used as first-line or primary therapy; **AND**
  - Used in combination with FOLFIRI; **OR**
  - Used in combination with FOLFOX *(Note: For colon cancer patients with left sided tumors only)*; **OR**
  - Used in combination with irinotecan after previous adjuvant FOLFOX or CapeOX within the past 12 months *(Note: For colon cancer patients with left sided tumors only)*; **OR**
- Used as subsequent therapy; **AND**
  - Used in combination with irinotecan for oxaliplatin- and/or irinotecan-refractory disease; **OR**
  - Used in combination with FOLFIRI for oxaliplatin-refractory disease; **OR**
  - Used in combination with FOLFOX for irinotecan-refractory disease; **OR**
  - Used as a single agent for oxaliplatin- and irinotecan-refractory disease OR irinotecan-intolerant disease; **OR**
- Used in combination with FOLFOX or FOLFIRI for one of the following *(Note: For colon cancer patients with left sided tumors only):*
  - Unresectable metastatic disease that remains unresectable after primary systemic therapy; **OR**
  - Unresectable metastatic disease in patients who have received adjuvant FOLFOX or CapeOX more than 12 months ago OR who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy; **OR**
  - Disease progression on non-intensive therapy with improvement in functional status (excluding patients previously treated with fluoropyrimidine); **OR**

- Patient has that is BRAF V600E mutation positive disease; **AND**
  - Used in combination with encorafenib; **AND**
    - Used as subsequent therapy for disease progression after at least one prior line of treatment in the advanced or metastatic disease setting; **OR**
    - Used as primary treatment for unresectable metastatic disease after previous adjuvant FOLFOX or CapeOX within the past 12 months

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- Used in one of the following regimens:
  - In combination with radiation therapy for first-line treatment of regionally or locally advanced disease; OR
  - As a single agent in recurrent or metastatic disease after failure on platinum-based therapy; OR
  - In combination with platinum-based therapy for first-line treatment of recurrent locoregional or metastatic disease; **AND**
- Patient has one of the following sub-types of SCCHN:
  - Cancer of the Glottic Larynx
  - Cancer of the Hypopharynx
    - Cetuximab may also be used as a single agent as sequential systemic therapy/radiation after induction chemotherapy
  - Cancer of the Lip (Mucosa)
  - Cancer of the Nasopharynx
  - Cancer of the Oral Cavity
  - Cancer of the Oropharynx
    - Cetuximab may also be used as a single agent as sequential systemic therapy/radiation after induction chemotherapy
  - Cancer of the Supraglottic Larynx
  - Ethmoid Sinus Tumors
  - Maxillary Sinus Tumors

- Very Advanced Head and Neck Cancer (i.e., newly diagnosed locally advanced T4b (M0) disease, newly diagnosed unresectable nodal disease, metastatic disease at initial presentation (M1), recurrent or persistent disease, or patients unfit for surgery)
  - Cetuximab may also be used as one of the following:
    - First-line therapy or subsequent therapy as a single agent for non-nasopharyngeal cancer
    - Subsequent therapy in combination with platinum-based therapy (except for locoregional recurrence without prior radiation therapy)
    - Sequential systemic therapy/radiation in patients with non-nasopharyngeal cancer as a single agent following induction therapy or combination systemic therapy for recurrent disease

Occult Primary Head and Neck Cancers

- Used as initial treatment as a single agent as sequential systemic therapy/radiation following induction chemotherapy

Squamous Cell Skin Cancer

- Used for inoperable or incompletely resected regional disease; **AND**
  - Used in combination with radiation therapy (RT); **OR**
  - Used as a single agent if curative RT not feasible AND if patient is ineligible for immune checkpoint inhibitors and clinical trials; **OR**
- Used for regional recurrence or distant metastases if patient is ineligible for immune checkpoint inhibitors and clinical trials

Penile Cancer

- Used as a single agent; **AND**
- Used as ~~for~~ subsequent therapy for metastatic disease

Non-Small Cell Lung Cancer (NSCLC)

- Patient has recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
- Used in combination with afatinib; **AND**
- Used as subsequent therapy for sensitizing EGFR mutation-positive tumors; **AND**
- Patient has progressed on EGFR tyrosine kinase inhibitor therapy (e.g., erlotinib, afatinib, gefitinib, dacomitinib, osimertinib, etc.); **AND**
  - Patient has asymptomatic disease, symptomatic brain lesions, or isolated symptomatic
  - systemic lesions; **OR**
  - Patient has multiple symptomatic systemic lesions; **AND**
    - Patient is T790M negative; **OR**
    - Patient is T790M positive and has progressed on second-line osimertinib therapy

**If confirmed using an FDA approved assay - http://www.fda.gov/companiondiagnostics*

RENEWAL CRITERIA

- Patient continues to meet indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc., identified in Initial Approval Criteria; **AND**

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: anaphylactic reactions, severe infusion reactions, cardiopulmonary arrest, pulmonary toxicity/interstitial lung disease, dermatologic toxicity, hypomagnesemia/electrolyte abnormalities, etc.

DOSAGE/ADMINISTRATION

INDICATION	DOSE
Colorectal Cancer	400 mg/m² loading dose intravenously, then 250 mg/m² intravenously every 7 days until disease progression or unacceptable toxicity; **OR** 500 mg/m² intravenously every 14 days until disease progression or unacceptable toxicity
NSCLC	500 mg/m² intravenously every 14 days until disease progression or unacceptable toxicity
SCCHN	In combination with radiation therapy: 400 mg/m² loading dose, then 250 mg/m² every 7 days for the duration of radiation therapy (6-7 weeks) Monotherapy or in combination with platinum-based therapy: 400 mg/m² loading dose, then 250 mg/m² every 7 days until disease progression or unacceptable toxicity
All other indications	400 mg/m² loading dose, then 250 mg/m² every 7 days until disease progression or unacceptable toxicity

LENGTH OF AUTHORIZATION

Coverage will be provided for six months and may be renewed unless otherwise specified.

- SCCHN in combination with radiation therapy: Coverage will be provided for the duration of radiation therapy (6-7 weeks).

DOSAGE LIMITS

Max Units (per dose and over time) [HCPCS Unit]:

Weekly	Every two weeks
– Load: 100 billable units x 1 dose – Maintenance Dose: 60 billable units every 7 days	120 billable units every 14 days

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health

plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

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EFFECTIVE DATE 6/2/2021

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