I. PURPOSE
To define and describe the accepted indications for Erbitux (cetuximab) usage in the treatment of cancer

II. DEFINITIONS

**Erbitux (cetuximab)**: is a recombinant monoclonal antibody that binds to the human epidermal growth factor receptor (EGFR) with high affinity. Binding to EGFR blocks phosphorylation and activation of receptor-associated kinases which results in cell growth inhibition, induction of apoptosis, and decreased vascular endothelial growth factor production. Erbitux (cetuximab) also induces internalization and degradation of EGFR, with resulting downregulation of cell surface receptors and reduced EGFR signaling. Mutation of the K-ras gene, a part of the EGFR signaling cascade, may affect response to Erbitux (cetuximab), in that mutated K-ras in the tumor cell may render EGFR inhibitors ineffective. Erbitux (cetuximab) is cell cycle phase-specific, arresting cells in the G1 phase.

Erbitux (cetuximab) is FDA approved for the treatment of members with head and neck and colorectal cancers. Non-FDA approved indication includes non-small cell lung cancer.

Erbitux (cetuximab) is available as 100 and 200 mg vials.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

**Inclusion Criteria**: Erbitux (cetuximab) may be considered medically necessary when any of the following selection criteria is met:

1. **Head and Neck Cancers**
   a. The member has advanced, recurrent, or persistent stage III-IV head and neck cancers and Erbitux (cetuximab) is being used in ONE of the following:
      i. As primary concurrent chemoradiation as a single agent for performance status 0-2 OR
ii. Sequential chemoradiation following induction chemotherapy for performance status 0-1 OR

iii. As recurrent therapy in combination with platinum based chemotherapy OR as a single agent.

2. Colorectal Cancer

a. The member has stage IV metastatic colorectal cancer and Erbitux (cetuximab) is being used for tumors expressing KRAS/NRAS wild-type gene as ONE of the following:

   i. Initial therapy (left-sided tumors for colon cancer only)

      1. In combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen for those who can tolerate intensive therapy.

   ii. Recurrent therapy (not previously treated with cetuximab or panitumumab)

      1. For disease previously treated with oxaliplatin based chemotherapy without irinotecan (i.e. FOLFOX OR CAPEOX/XELOX): used in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) OR irinotecan.

      2. For disease previously treated with irinotecan based chemotherapy without oxaliplatin (i.e. FOLFIRI): used in combination with irinotecan.

      3. In combination with irinotecan for member who has failed or cannot tolerate irinotecan and oxaliplatin based regimens.

      4. In combination with irinotecan for disease previously treated with FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen.

3. Non-Small Cell Lung Cancer (NSCLC)

a. The member has NSCLC Erbitux (cetuximab) is being used in combination with afatinib as subsequent therapy for metastatic disease in patients with a known sensitizing EGFR mutation with the following:

   i. Who have progressed on EGFR tyrosine kinase inhibitor therapy for asymptomatic disease (without rapid radiologic progression or threatened organ function), symptomatic brain lesions, or isolated symptomatic systemic lesions OR

   ii. Who are T790M negative, have progressed on EGFR tyrosine kinase inhibitor therapy, and have multiple symptomatic systemic lesions.

Exclusion Criteria: Erbitux (cetuximab) is not considered medically necessary when any of the following selection criteria is met:

1. Erbitux (cetuximab) is being used in colorectal cancer for any of the following:
• Tumor with KRAS/NRAS mutations
• In member who has disease progression on Erbitux (cetuximab) or who has failed Vectibix (panitumumab)
• Used in combination with FOLFOX as second line therapy

2. Dosing exceeds single dose limit of Erbitux (cetuximab) 400 mg/m$^2$ weekly OR 500 mg/m$^2$ every 2 weeks.

3. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Erbitux (cetuximab) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. Dosage and Administration
   a. Head and Neck/Colorectal/NSCLC: 400 mg/m$^2$ initial IV loading dose over 120 min followed by weekly doses of 250 mg/m$^2$ IV over 60 min. Alternate dosing in colon or NSCLC cancer (without a loading dose) consists of 500 mg/m$^2$ every 2 weeks.

2. Dosage Adjustments
   a. Dermatologic toxicities (severe, grade 3 or 4 acne form rash): delay for 1 to 2 weeks; if improved, restart at 250 mg/m$^2$ after the first occurrence, 200 mg/m$^2$ after the second occurrence, and 150 mg/m$^2$ after the third occurrence; cetuximab should be discontinued if a member does not improve from a previous episode or has a fourth occurrence.
   b. Infusion-related toxicities: decrease infusion rate by 50% for grade 1 or 2 (mild to moderate) infusion-related reactions and non-serious grade 3 or 4 infusion reactions; permanently discontinue cetuximab in members experiencing a serious reaction that requires medical intervention and/or hospitalization.
   c. Pulmonary toxicities: interrupt for acute onset or worsening of pulmonary symptoms; permanently discontinue cetuximab in members if interstitial pulmonary lung disease (ILD) is confirmed.

3. Monitoring
   a. Laboratory Parameters
      Conduct pretreatment testing for overexpression of epidermal growth factor receptor (EGFR) in tumor specimens prior to institution of therapy.
      i. All members with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody treatment should have the tumor tested for KRAS mutations in a laboratory accredited by the Clinical Laboratory Improvement Amendments (CLIA). If KRAS mutation in codon 12 or 13 is identified, then the member should not receive anti-EGFR antibody therapy.
      ii. Pretreatment testing is not usually required in head and neck cancer patients.
iii. Pretreatment screening can be accomplished by immunohistochemistry, fluorescence in situ hybridization, solid matrix-blotting, and/or ELISA; immunohistochemistry is used most often, and is highly reliable.

iv. Monitor electrolytes periodically for hypomagnesemia, hypocalcemia, and hypokalemia throughout treatment and for 8 weeks following the completion of therapy.

b. Physical Findings

i. Monitor members for infusion reaction for 1 hour after the completion of the infusion. If a member requires treatment for an infusion reaction, monitor until resolution of the event is confirmed. Some serious or fatal (eg, bronchospasm, stridor, hypotension, shock, loss of consciousness, myocardial infarction, cardiac arrest), have been reported; monitoring recommended and immediately and permanently discontinue if serious.

ii. Cardiopulmonary arrest and/or sudden death have been reported in patients with squamous cell carcinoma of the head and neck treated with concomitant radiation therapy or platinum-based therapy with 5-fluorouracil, with an increased risk in patients with a history of arrhythmias, congestive heart failure, or coronary artery disease; monitoring recommended.

iii. Concomitant use with radiation therapy and cisplatin increased incidence of fatal and serious adverse events (e.g., cardiac events, electrolyte disturbances) compared with radiation and cisplatin alone.

iv. Electrolyte abnormalities (e.g., hypomagnesemia, hypocalcemia, hypokalemia) have occurred; monitoring recommended.

v. Interstitial lung disease (ILD) (including 1 fatality), has been reported; permanently discontinue for confirmed ILD.

vi. Assess members for dermatologic toxicities and infectious sequelae during therapy.

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

VII. REFERENCES

1. Erbitux (cetuximab) prescribing information. ImClone LLC, Branchburg, NJ 2018.