Cetuximab (Erbitux®)

Prior Authorization Drug Coverage Policy

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Lines of Business: Commercial
Policy type: Prior Authorization

This Drug Coverage Policy provides parameters for the coverage of Cetuximab (Erbitux®). Consideration of medically necessary indications are based upon U.S. Food and Drug Administration (FDA) indications, recommended uses within the Centers of Medicare & Medicaid Services (CMS) five recognized compendia, including the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (Categories 1 and 2A), and peer-reviewed scientific literature eligible for coverage according to the CMS, Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 titled, "Off-Label Use of Anti-Cancer Drugs and Biologics." This policy evaluates whether the drug therapy is proven to be effective based on published evidence-based medicine.

Drug Description[1]

Cetuximab is a recombinant human/mouse chimeric monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands. Binding 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. EGFR signal transduction results in RAS wild-type activation; cells with RAS mutations appear to be unaffected by EGFR inhibition.

Indications

FDA Indications[1]

Cetuximab (Erbitux®) is FDA indicated for the following:

- **Squamous cell cancer of the head and neck:**
  - As a single agent for recurrent or metastatic disease after platinum-based chemotherapy failure **OR**
  - In combination with radiation therapy as initial treatment of locally or regionally advanced disease **OR**
  - In combination with platinum and fluorouracil-based chemotherapy as first-line treatment of locoregional or metastatic disease.

Recommended dosage: 400 mg/m^2 IV loading dose, followed by weekly doses of 250 mg/m^2 IV.

- **Metastatic colorectal cancer**:
    - Treatment of KRAS wild-type (without mutation), EGFR-expressing metastatic colorectal cancer as determined by an approved test:
        - In combination with FOLFIRI (irinotecan, fluorouracil, and leucovorin) as first-line treatment **OR**
        - In combination with irinotecan (in patients refractory to irinotecan-based chemotherapy) **OR**
        - As a single agent in patients who have failed irinotecan- and oxaliplatin-based chemotherapy or who are intolerant to irinotecan **OR**
        - In combination with encorafenib, for the treatment of adult patients with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Recommended dosage: 400 mg/m^2 IV loading dose, followed by weekly doses of 250 mg/m^2 IV.

NCCN Compendium Supported Indications[2]

- Colon cancer.
- Head and neck cancer.
- Non-small cell lung cancer.
- Penile cancer.
- Rectal cancer.
- Squamous cell skin cancer.

Coverage Determinations

Cetuximab (Erbitux®) will require prior authorization. This agent is considered medically necessary for the following oncology indications if all criteria below are met:

Head and Neck Cancer

1) The member has metastatic head and neck cancer at initial presentation, recurrent/persistent disease with distant metastases, unresectable locoregional recurrence with prior radiation therapy, or unresectable second primary with prior RT **AND**
    - Cetuximab is being used as first-line or subsequent-line option in patients with non-nasopharyngeal cancer in combination with:
        - Fluorouracil and cisplatin **OR**
        - Fluorouracil and carboplatin **OR**
        - Docetaxel and cisplatin **OR**
        - Docetaxel and carboplatin **OR**
        - Paclitaxel and cisplatin **OR**
        - Paclitaxel and carboplatin **OR**

        - Cisplatin alone.
2) The member has a diagnosis of non-nasopharyngeal head and neck cancer with resectable locoregional recurrence without prior radiation therapy **AND**
    - Cetuximab is being given in combination with:
        - Fluorouracil and cisplatin **OR**
        - Fluorouracil and carboplatin **OR**
        - Docetaxel and cisplatin **OR**
        - Docetaxel and carboplatin **OR**
        - Paclitaxel and cisplatin **OR**
        - Paclitaxel and carboplatin **OR**
        - Cisplatin alone
3) The member has a diagnosis of head and neck cancer **AND**
    - Cetuximab is being used as post-operative systemic therapy/radiation.
4) The member has a diagnosis of metastatic head and neck cancer, with nasopharyngeal disease **AND**
    - Cetuximab is being used as part of first-line platinum-based chemotherapy in combination with carboplatin.
5) The member has non-nasopharyngeal head and neck cancer **AND**
    - Cetuximab is being used as a first-line or subsequent-line option as a single agent for:
        - Newly diagnosed T4b, N0-3, M0 disease, unresectable nodal disease with no metastases, unresectable locoregional recurrence without prior radiation therapy, or non-metastatic disease for patients who are unfit for surgery **OR**
        - Metastatic disease at initial presentation, recurrent/persistent disease with distant metastases, unresectable locoregional recurrence with prior radiation therapy, or unresectable second primary with prior RT.
6) The member has head and neck cancer of the oropharynx **AND**
    - Cetuximab is being used as sequential systemic therapy/radiation as a single agent given weekly following induction chemotherapy **AND**
    - The member has p16-negative disease **AND**
    - The member has T3-4a, N0-1 disease **OR**
    - The member has T1-4, N2-3 disease.
7) The member has advanced head and neck cancer **AND**
    - Cetuximab is being used as sequential systemic therapy/radiation as a single agent given weekly following induction therapy **AND**
    - The member has non-nasopharyngeal cancer **AND**
    - The member has newly diagnosed T4b, N0-3, M0 disease **OR**
    - The member has unresectable nodal disease with no metastases **OR**
    - The member has unresectable locoregional recurrence and have no received prior RT.
8) The member has advanced head and neck cancer **AND**

- The member has nasopharyngeal disease **AND**
- Cetuximab is being used in combination with carboplatin as first-line or subsequent-line option in patients **AND**
- The member has recurrent/persistent disease with distant metastases, unresectable locoregional recurrence with prior RT, or second primary with prior RT.

9) The member has advanced head and neck cancer **AND**
   - The member has non-nasopharyngeal cancer **AND**
   - Cetuximab is being used as sequential systemic therapy/radiation as a single agent given weekly following combination systemic therapy for resectable locoregional recurrence without prior radiation therapy.
10) The member has head and neck cancer of the oropharynx **AND**
   - Cetuximab is being used as sequential systemic therapy/radiation **AND**
   - Cetuximab is given as a single agent **AND**
   - Cetuximab is being given weekly following induction chemotherapy **AND**
   - The member is p16 (HPV)-positive **AND**
   - The member has T1-2, N1 (single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm), T1-2, N2 or T3, N0-2 disease **OR**
   - The member has T1-3, N3 or T4, N0-3 disease.
11) The member has head and neck cancer – occult primary **AND**
   - Cetuximab is being used as initial definitive treatment as a single agent for N2-3 disease as sequential systemic therapy/radiation given weekly following induction chemotherapy.
12) The member has head and neck cancer of the hypopharynx **AND**
   - Cetuximab is being used as sequential systemic therapy/radiation as a single agent given weekly for T4a, N0-3 disease:
     - Following a partial response at the primary site and stable or improved disease in the neck following induction chemotherapy **OR**
     - May be considered following a complete response at the primary site and stable or improved disease in the neck following induction chemotherapy.

Recommended dosage: 400 mg/m^2 IV loading dose, followed by weekly doses of 250 mg/m^2 IV.

Metastatic Colorectal Cancer

1) The member has a diagnosis of colorectal cancer **AND**
   - The member has a documented intolerance to panitumumab **AND**
   - The member has KRAS/NRAS/BRAF wild-type disease **AND**
   - Cetuximab is being used as subsequent therapy for progression of advanced or metastatic disease which was not previously treated with cetuximab or panitumumab:
     - In combination with irinotecan, FOLFIRI (fluorouracil, leucovorin, and irinotecan), or as a single agent for patients who cannot tolerate irinotecan, if previously treated with oxaliplatin-based therapy without irinotecan **OR**

- In combination with irinotecan, FOLFOX (fluorouracil, leucovorin, and oxaliplatin), or as a single agent for patients who cannot tolerate irinotecan if previously treated with irinotecan-based therapy without oxaliplatin **OR**
- In combination with irinotecan or as a single agent for patients who cannot tolerate irinotecan if previously treated with oxaliplatin and irinotecan **OR**
- In combination with irinotecan or as a single agent for patients who cannot tolerate irinotecan if previously treated with a fluoropyrimidine without irinotecan or oxaliplatin followed by FOLFOX or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab.

2) The member has a diagnosis of colorectal cancer **AND**
   - The member has a documented intolerance to panitumumab **AND**
   - The member is BRAF V600E mutation positive **AND**
   - Cetuximab is being used as primary treatment in combination with encorafenib **AND**
   - The member has unresectable metachronous metastases **AND**
   - The member has received previous adjuvant FOLFOX or CapeOX within the past 12 months.
3) The member has a diagnosis of colon cancer **AND**
   - The member has a documented intolerance to panitumumab **AND**
   - Cetuximab is being used for KRAS/NRAS/BRAF wild-type gene and left-sided only tumors **AND**
   - Cetuximab is being used in combination with FOLFOX or FOLFIRI in patients appropriate for intensive therapy:
     - As primary treatment for locally unresectable or medically inoperable disease **OR**
     - For unresectable synchronous liver and/or lung metastases that remain unresectable after primary systemic therapy **OR**
     - As primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction **OR**
     - For synchronous unresectable metastases of other sites **OR**
     - As primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy **OR**
     - For unresectable metachronous metastases that remain unresectable after primary treatment **OR**
     - The member has progressed on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status.
4) The member has a diagnosis of colorectal cancer **AND**
   - The member has a documented intolerance to panitumumab **AND**
   - The member is BRAF V600E mutation positive **AND**

- Cetuximab is being used as subsequent therapy in combination with encorafenib for progression of advanced or metastatic disease in patients previously treated with:
  - Oxaliplatin-based therapy without irinotecan **OR**
  - Irinotecan-based therapy without oxaliplatin **OR**
  - Oxaliplatin and irinotecan **OR**
  - A fluoropyrimidine without irinotecan or oxaliplatin **OR**
  - A fluoropyrimidine without irinotecan or oxaliplatin followed by FOLFOX or CapeOX with or without bevacizumab.

5) The member has a diagnosis of colorectal cancer **AND**
   - The member has a documented intolerance to panitumumab **AND**
   - The member has KRAS/NRAS/BRAF wild-type gene and left-sided tumors only (left-sided tumors applies to colon cancer only) **AND**
   - Cetuximab is being used as primary treatment for patients with unresectable metachronous metastases **AND**
   - The member has received previous adjuvant FOLFOX or CapeOX within the past 12 months:
     - In combination with irinotecan **OR**
     - In combination with FOLFIRI.
6) The member has a diagnosis of colorectal cancer **AND**
   - The member has a documented intolerance to panitumumab **AND**
   - Cetuximab is being used as primary treatment for unresectable synchronous liver and/or lung metastases **AND**
   - The member has KRAS/NRAS/BRAF wild-type gene and left-sided tumors only **AND**
   - Cetuximab is being used in combination with:
     - FOLFOX **OR**
     - FOLFIRI.
7) The member has a diagnosis of rectal cancer **AND**
   - The member has a documented intolerance to panitumumab **AND**
   - The member has KRAS/NRAS/BRAF wild-type gene tumor **AND**
   - Cetuximab is being used in combination with FOLFOX or FOLFIRI in patients appropriate for intensive therapy:
     - As primary treatment for T3, N Any; T1-2, N1-2; T4, N Any; or locally unresectable or medically inoperable disease if resection is contraindicated following neoadjuvant therapy **OR**
     - For synchronous liver only and/or lung only metastases that are unresectable or medically inoperable and remain unresectable (with no progression of primary tumor) after primary systemic therapy **OR**
     - Following palliative radiation therapy or chemo/RT for synchronous liver only and/or lung only metastases that are unresectable or medically inoperable and remain unresectable (with progression of primary tumor) after primary systemic therapy **OR**
     - As primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction **OR**

- As primary treatment for synchronous unresectable metastases of other sites **OR**
- As primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months, who have received previous 5-FU/LV or capecitabine therapy, or who have not received any previous chemotherapy **OR**
- For unresectable metachronous metastases that remain unresectable after primary treatment **OR**
- The member has progressed on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status.

Recommended dosage: 400 mg/m^2 IV loading dose, followed by weekly doses of 250 mg/m^2 IV.

Non-Small Cell Lung Cancer (NSCLC)

- The member has a diagnosis of recurrent, advanced, or metastatic NSCLC with a known sensitizing EGFR mutation **AND**
- Cetuximab is being given in combination with afatinib as subsequent therapy **AND**
- The member has progressed on EGFR tyrosine kinase inhibitor therapy for asymptomatic disease, symptomatic brain lesions, or isolated symptomatic systemic lesions **OR**
- The member is T790M negative, has progressed on EGFR tyrosine kinase inhibitor therapy, and has multiple symptomatic systemic lesions.

Recommended dosage: 500 mg/m^2 IV every 2 weeks.

Penile Cancer

- The member has a diagnosis of metastatic penile cancer **AND**
- Cetuximab is being used as a single agent as subsequent-line systemic therapy.

Recommended dosage: 400 mg/m^2 IV loading dose, followed by weekly doses of 250 mg/m^2 IV.

Squamous Cell Skin Cancer

- The member has a diagnosis of squamous cell skin cancer **AND**

- The member has inoperable or incompletely resected regional disease and is receiving cetuximab for use with radiation therapy (RT) **OR**
- The member has inoperable or incompletely resected regional disease and is receiving cetuximab as systemic therapy alone if curative RT is not feasible and if ineligible for immune checkpoint inhibitors and clinical trials **OR**
- The member has regional recurrence or distant metastases and is ineligible for immune checkpoint inhibitors and clinical trials.

Recommended dosage: 400 mg/m^2 IV loading dose, followed by weekly doses of 250 mg/m^2 IV.

All indications:

- Cetuximab (Erbitux®) will be approved through clinical review up to a 12-month duration.

Coverage Limitations

Treatment with Cetuximab (Erbitux®) is not considered medically necessary for members with the following concomitant conditions:

- Not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.
- The member has had disease progression on panitumumab or cetuximab.
- Cetuximab may not be used in conjunction with a bevacizumab product.
- Indications not supported by NCCN category 2A or higher recommendations may not be considered medically necessary

Contraindications/Warnings/Precautions[1]

- There are no contraindications listed in the US manufacturer's labeling.
- Warnings/precautions:
    - Infusion reactions [**Boxed warning**]
    - Cardiopulmonary arrest [**Boxed warning**]
    - Pulmonary toxicity
    - Dermatologic toxicity
    - Hypomagnesemia and accompanying electrolyte abnormalities
    - Increased tumor progression, increased mortality, or lack of benefit observed in patients with Ras-mutant mCRC
    - Embryo-fetal toxicity

For specific recommendations on contraindications, warnings and precautions, patient monitoring, and on dose adjustments and discontinuation, please refer to the current prescribing information.

Billing

- Description: injection, cetuximab, 10 mg
    - HCPCS: J9055

Disclaimer

Drug Coverage Policies are developed as needed, regularly reviewed, updated at least annually, and are subject to change. Other policies and coverage determination guidelines may apply. Federal and state regulatory requirements and member specific benefit plan documents, if applicable, must be reviewed prior to this Drug Coverage Policy. This Drug Coverage Policy is for informational purposes only and does not constitute medical advice or dictate how providers should practice medicine. This policy should not be reproduced, stored in a retrieval system, or altered from its original form without written permission from Oncology Analytics, Inc.

References

1. Erbitux [package insert]. Eli Lilly and Co., Indianapolis, IN. Available at: http://pi.lilly.com/us/erbitux-uspi.pdf
2. Cetuximab. NCCN Drugs & Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/