Pharmacy Management Drug Policy

SUBJECT: Erbitux (cetuximab) – For Managed Medicaid and Child Health Plus
POLICY NUMBER: PHARMACY-14
EFFECTIVE DATE: 9/09
LAST REVIEW DATE: 5/1/2019

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. Medical or drug policies apply to commercial and Health Care Reform products only when a contract benefit for the specific service exists.

DESCRIPTION:

Cetuximab is a recombinant humanized monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of EGF and other ligands. Its binding results in inhibition of cell growth, induction of apoptosis, and a decrease in the vascular endothelial growth factor production.

The 2008 National Comprehensive Cancer Network (NCCN) guidelines for both colon and rectal cancer were updated to include the addition of Kirsten rat sarcoma viral oncogene (KRAS) gene testing in the workup for all patients with stage IV disease. The guidelines state that cetuximab and panitumumab are only indicated for patients with tumors that express the wild-type KRAS gene.

In summary, clinical trial data show that patients with KRAS-mutated metastatic CRC do not benefit from cetuximab or panitumumab, either as monotherapy or in combination with other treatment regimens. These data support the use of KRAS mutation analysis of tumor DNA before considering use of cetuximab or panitumumab in a treatment regimen. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs and unnecessary drug toxicities and expedite the use of alternative therapies. Thus, KRAS mutation analysis may be considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic CRC. K-RAS mutations are found in 30 to 45% of all colorectal tumors.

Cetuximab is FDA indicated and/or NCCN supported for use in several non-CRC cancers. RAS mutations are rare in these other cancer types. RAS mutation testing is, therefore, not of significant clinical value and is not required for non-CRC cancer types.

POLICY:

Based upon our assessment and review of the peer-reviewed literature, Erbitux has been medically proven to be effective and therefore, **medically appropriate** under the following conditions:

***Note the following testing required for colorectal cancers:**

A. RAS and BRAF mutation analyses are required for all mCRC requests **AND**
B. Testing must reveal wild-type RAS and BRAF expression (versus mutant-type *KRAS/NRAS/BRAF*). Wild-type RAS is defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use. Erbitux is not indicated for the treatment of patients with *RAS/BRAF*-mutant mCRC or for whom *RAS/BRAF* mutation status is unknown.
C. Request must also meet **one** of the following conditions:

1. Colon cancer

1. in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment **OR**
2. in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy **OR**
3. as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan **OR**
4. Therapy for *KRAS/NRAS/BRAF* wild-type gene and left-sided only tumors in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
    a. as primary treatment for locally unresectable or medically inoperable disease
    b. for unresectable synchronous liver and/or lung metastases that remain unresectable after primary systemic therapy
    c. as primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction
    d. for synchronous unresectable metastases of other sites
    e. 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
    f. for unresectable metachronous metastases that remain unresectable after primary treatment **OR**

5. Primary treatment for unresectable synchronous liver and/or lung metastases (*KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only) in combination with
    a. FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen
    b. FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen **OR**
6. Primary treatment for patients with unresectable metachronous metastases (*KRAS/NRAS/BRAF* wild-type gene and left-sided tumors only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months
    a. in combination with irinotecan
    b. in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen **OR**
7. Primary treatment in combination with irinotecan and vemurafenib for patients with unresectable metachronous metastases (BRAF V600E mutation positive) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months **OR**

8. Subsequent therapy for progression of unresectable advanced or metastatic disease (*KRAS/NRAS/BRAF* wild-type only) not previously treated with cetuximab or panitumumab
    a. In combination with irinotecan or with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if previously treated with oxaliplatin-based therapy without irinotecan
    b. In combination with irinotecan if previously treated with irinotecan-based therapy without oxaliplatin
    c. In combination with irinotecan if previously treated with FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen
    d. In combination with irinotecan if previously treated with a fluoropyrimidine without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab **OR**
9. Subsequent therapy in combination with irinotecan and vemurafenib for progression of unresectable advanced or metastatic disease (BRAF V600E mutation positive) not previously treated with cetuximab or panitumumab, in patients previously treated with
    a. oxaliplatin-based therapy without irinotecan
    b. irinotecan-based therapy without oxaliplatin
    c. FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen
    d. a fluoropyrimidine without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab **OR**

2. Squamous Cell Carcinoma of the Head and Neck

1. in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck **OR**
2. in combination with platinum-based therapy with 5-FU for the first--line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck **OR**
3. as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed **OR**
4. Cancer of the Oropharynx –
    A. Primary concurrent chemoradiation as a single agent for p16-negative
        I. T3-4a, N0-1 disease
        II. any T, N2-3 disease
    B. Primary concurrent chemoradiation as a single agent for p16 (HPV)-positive
        I. cT3-4, cN0-1 (single node ≤3 cm) disease
        II. any T, cN1 (single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm), cN2-3 disease
    C. Sequential chemoradiation as a single agent given weekly following induction chemotherapy for p16-negative

I. T3-4a, N0-1 disease
II. any T, N2-3 disease

D. Sequential chemoradiation as a single agent given weekly following induction chemotherapy for p16 (HPV)-positive
I. cT3-4, cN0-1 (single node ≤3 cm) disease
II. any T, cN1 (single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm), cN2-3 disease

5. Cancer of the hypopharynx –
A. Primary concurrent chemoradiation as a single agent for
I. T1, N+ disease
II. T2-3, any N disease requiring (amenable to) pharyngectomy with partial or total laryngectomy
B. Sequential chemoradiation as a single agent given weekly for requi for T4a, any N disease
I. following a partial response at the primary site and stable or improved disease in the neck following induction chemotherapy
II. may be considered following a complete response at the primary site and stable or improved disease in the neck following induction chemotherapy
6. Cancer of the Nasopharynx –
A. First-line platinum-based chemotherapy in combination with carboplatin for any T, any N, M1 disease
7. Cancer of the Glottic Larynx –
A. Primary concurrent chemoradiation as a single agent for
I. for T3, N0-3 disease requiring (amenable to) total laryngectomy
II. may be considered for selected T4a patients who decline surgery
8. Cancer of the Supraglottic Larynx –
A. Primary concurrent chemoradiation as a single agent
I. for T3, N0 and most T3, N2-3 disease requiring (amenable to) total laryngectomy
II. for T1-2, N+ and selected T3, N1 disease amenable to larynx-preserving (conservation) surgery
III. may be considered for T4a, N0-3 disease for patients who decline surgery
9. Very Advanced Head and Neck Cancer –
A. Primary concurrent chemoradiation for non-nasopharyngeal (disease in the orphyarynx, hypopharynx, or larynx) cancer as a single agent for
I. newly diagnosed T4b, any N, M0 disease, unresectable nodal disease with no metastases, for patients who are unfit for surgery, or unresectable locoregional recurrence without prior radiation therapy (RT) and performance status (PS) 0-2

II. metastatic (M1) disease at initial presentation or recurrent/persistent disease with distant metastases and PS 0-1
III. resectable locoregional recurrence without prior RT
IV. unresectable locoregional recurrence or second primary with prior RT

B. Sequential chemoradiation as a single agent given weekly following induction chemotherapy in patients with non-nasopharyngeal cancer for
I. newly diagnosed T4b, any N, M0 disease, unresectable nodal disease with no metastases, for patients who are unfit for surgery, or
II. unresectable locoregional recurrence in patients without prior radiation therapy and performance status (PS) 0-1
III. resectable locoregional recurrence without prior RT

C. Systemic therapy as a first-line, second-line, or subsequent therapy option as a
I. single agent for patients with non-nasopharyngeal cancer with newly diagnosed T4b, any N, M0 disease, unresectable nodal disease with no metastases, unresectable locoregional recurrence without prior radiation therapy (RT), or for patients who are unfit for surgery and performance status (PS) 3
II. single agent (non-nasopharyngeal cancer) in PS 0-2 patients or in combination (PS 0-1) with carboplatin (nasopharyngeal cancer) or cisplatin (non-nasopharyngeal cancer) alone, or in combination with cisplatin or carboplatin and either fluorouracil, docetaxel, or paclitaxel (non-nasopharyngeal cancer) for metastatic (M1) disease at initial presentation, recurrent/persistent disease with distant metastases, or unresectable locoregional recurrence or second primary with prior RT

10. Occult Primary –
A. Initial definitive treatment as a single agent
I. given weekly for sequential chemoradiation following induction chemotherapy for N2-3 disease

3. Non-Small Cell Lung Cancer –

1. May be considered in combination with afatinib as subsequent therapy for metastatic disease in patients with a known sensitizing EGFR mutation
A. 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
I. who are T790M negative, have progressed on EGFR tyrosine kinase inhibitor therapy, and have multiple symptomatic systemic lesions

4. Penile Cancer –

1. Consider in select patients as a single agent as subsequent-line systemic therapy for metastatic disease

5. **Rectal Cancer –**

1. Therapy for *KRAS/NRAS/BRAF* wild-type gene tumors in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
    A. 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
    B. 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
    C. following short-course radiation therapy (RT) 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
    D. as primary treatment for synchronous abdominal/peritoneal metastases that are non-obstructing, or following local therapy for patients with existing or imminent obstruction
    E. as primary treatment for synchronous unresectable metastases of other sites
    F. 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
    G. for unresectable metachronous metastases that remain unresectable after primary treatment
2. Primary treatment for synchronous liver only and/or lung only metastases (*KRAS/NRAS/BRAF* wild-type gene only) that are unresectable or medically inoperable in combination with
    A. FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
    B. FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen
3. Primary treatment for patients with unresectable metachronous metastases (*KRAS/NRAS/BRAF* wild-type gene only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months
    A. in combination with irinotecan
    B. in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
4. Primary treatment in combination with irinotecan and vemurafenib for patients with unresectable metachronous metastases (BRAF V600E mutation positive) and

previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months

5. Subsequent therapy for progression of unresectable advanced or metastatic disease (*KRAS/NRAS/BRAF* wild-type gene only) not previously treated with cetuximab or panitumumab
    A. in combination with irinotecan or with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if previously treated with oxaliplatin-based therapy without irinotecan
    B. in combination with irinotecan if previously treated with irinotecan-based therapy without oxaliplatin
    C. in combination with irinotecan if previously treated with FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen
    D. in combination with irinotecan if previously treated with a fluoropyrimidine without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab
6. Subsequent therapy in combination with irinotecan and vemurafenib for progression of unresectable advanced or metastatic disease (BRAF V600E mutation positive) not previously treated with cetuximab or panitumumab, in patients previously treated with
    A. oxaliplatin-based therapy without irinotecan
    B. irinotecan-based therapy without oxaliplatin
    C. FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen
    D. a fluoropyrimidine without irinotecan or oxaliplatin followed by FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) with or without bevacizumab

6. Squamous Cell Skin Cancer –

1. Treatment for inoperable positive regional lymph nodes, regional recurrence, or distant metastases.

POLICY GUIDELINES:

1. Prior-authorization is contract dependent.
    a. This policy currently applies only to the Medicaid Managed Care (MMC) line of business.
2. Unless otherwise stated above within the individual drug criteria, **approval time periods** are listed in the table below.
    - Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary. Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e.; generics, biosimilars, or other guideline-supported treatment options). Requested dosing must continue to be consistent with FDA-approved or off-label/guideline-supported dosing recommendations.

Line of Business	Initial approval	Continued approval
Medicaid Managed Care (MMC) / Child Health Plus (CHP)	6 months	12 months

3. Dosing should not exceed 250 mg/m^2 weekly for HNSCC or CRC. For other indications, the dosing must be consistent with current practice guidelines or the peer-reviewed literature that provided the support for such use.
4. The safety and effectiveness of Erbitux in pediatric patients have not been established. Erbitux should not be used in patients under 18 years of age.

CODES: Number

Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

HCPCS: J9055 Erbitux

UPDATES:

Date	Revision
5/2019	P&T Approval
5/2019	Revised
10/2018	Revised
9/2018	Reactivated
4/2017	Archived
8/2016	Revised
9/2015	Revised
3/2015	Revised
11/2013	Revised
10/2012	Revised
6/2012	Revised
11/2011	Revised
2/2011	Revised
12/2010	Reviewed
6/2010	Revised
3/2010	Revised
2/2010	Revised
9/2009	Created

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