I. Description

Erbitux (Cetuximab) is a recombinant monoclonal IgG1 antibody that binds to and inhibits the biologic activity of the human epidermal growth factor receptor (EGFR). It is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma used in combination with irinotecan, in patients who are refractory to irinotecan-based chemotherapy; as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy; in combination with radiation therapy, for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck and as a single agent 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.

Recent studies have identified a gene KRAS that when mutated, is resistant to EGFR-inhibitors. It is estimated that KRAS is mutated in 20 to 50% of colon tumors. The studies analyzed the efficacy of EGFR-inhibitors in patients with wild type versus mutated KRAS in metastatic colorectal cancer. The results have consistently shown a lack of clinical response to cetuximab and panitumumab in patients with mutated KRAS, with tumor response and prolongation of progression free and overall survival observed only in wild-type KRAS patients. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs, avoid exposure to unnecessary drug toxicities and expedite the use of the best available alternative therapy. Therefore, cetuximab for the treatment of metastatic colorectal cancer is only recommended for patients with tumors that express the wild-type KRAS gene.

II. Criteria/Guidelines

A. Cetuximab is covered (subject to Limitations/Exclusions and Administrative Guidelines) when recommended by an oncologist for the following indications:

1. Metastatic colorectal cancer for tumors expressing the KRAS wild-type gene when used:
   a. In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy.
b. As a single-agent after failure of both irinotecan and oxaliplatin-based regimens.

c. As a single-agent for patients who are intolerant to irinotecan-based regimens.

d. In the initial therapy in combination with FOLFIRI regimen for those who can tolerate intensive therapy

e. In combination with fluorouracil, leucovorin and irinotecan (FOLFIRI) regimen as:

   i. Perioperative therapy for patients with synchronous liver and/or lung metastases or resectable metachronous metastases.

   ii. Therapy for patients with unresectable synchronous liver and/or lung metastases, with synchronous abdominal/peritoneal metastases, or with unresectable metachronous metastases.

f. For patients with unresectable advanced or metastatic disease who have not previously received cetuximab or panitumumab when used:

   i. As a single-agent or in combination with irinotecan after first progression, in patients previously receiving irinotecan based regimens.

   ii. In combination with FOLFIRI after first progression in patients who previously received oxaliplatin based regimens with our without bevacizumab.

   iii. As a single-agent or in combination with irinotecan after second progression.

2. Squamous cell carcinoma of the head and neck cancers when used:

   a. In combination with radiation therapy for the initial treatment of locally or regionally advanced disease.

   b. As a single-agent for patients with recurrent or metastatic disease for whom prior platinum-based therapy has failed.

3. Squamous cell skin cancer for regional recurrence or distant metastases.

4. Non-small cell lung cancer (NSCLC) when used:

   a. As first-line therapy for recurrence or metastasis in combination with vinorelbine and cisplatin in patients with performance status 0-1.

   b. As a single-agent for continuation maintenance therapy if given first line with chemotherapy for recurrence or metastasis in patients with performance status 0-2 who achieve tumor response or stable disease following first-line chemotherapy.

5. Bone cancer when used in combination with erlotinib for the treatment of recurrent disease.

B. For all indications, HMSA follows NCCN level 1 or 2A and/or DrugDex level I or IIA recommendations.

C. Continuation of therapy is covered (subject to Limitations/Exclusions and Administrative Guidelines) when the initial therapy has been approved and the patient shows no progression of disease.

III. Limitations/Exclusions

   A. Cetuximab is not covered if the patient has had progression of disease while on cetuximab.
B. Cetuximab is not covered if the patient has had progression of disease while being treated with panitumumab.

C. Cetuximab for the treatment of colorectal cancer is not covered in patients with tumors expressing the KRAS mutation.

IV. Administrative Guidelines

A. Precertification is required for the initial three months of therapy. To precertify, please complete HMSA’s Drug Review Request and mail or fax the form as indicated. Include the following documentation:

1. Clinical notes that include the history of previous treatment
2. Current oncology notes
3. Pathology reports
4. Imaging studies
5. CEA for colorectal cancer
6. KRAS gene test results for colorectal cancer

B. Precertification is required for continuation of therapy for up to an additional three months. The following documentation must be submitted:

1. Current oncology notes documenting the patient’s response to treatment showing no disease progression.
2. Objective findings demonstrating no progression of disease (i.e., CEA and/or imaging).

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<th>HCPCS</th>
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V. Scientific Background

The efficacy and safety of cetuximab was evaluated in two clinical trials. Investigators in one randomized, controlled trial with 329 patients looked at cetuximab alone or in combination with irinotecan. A second study looked at cetuximab in combination with irinotecan in 138 patients in which all patients received both drugs. Cetuximab was further evaluated as a single agent in a third clinical trial with 57 patients. Safety data from an additional 111 patients treated only with cetuximab was also reviewed. All of the trials included patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving irinotecan.

For patients with tumors that express EGFR and who no longer responded to treatment with irinotecan alone or in combination with other chemotherapy drugs, the combination treatment of cetuximab and irinotecan shrank tumors in 22.9 percent of patients and delayed tumor growth by approximately 4.1 months. For patients who received cetuximab alone, the tumor response rate was 10.8 percent and tumor growth was delayed by 1.5 months.

Bonner et. al. (2006) lead a multi-national clinical trial to evaluate the addition of cetuximab to radiation therapy in the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (stage III/IV) (spread of cancer from site of origin but not to distant sites in the body).
in 424 patients. Approximately half the patients were treated with cetuximab and high-dose radiation, the other half received high-dose radiation only.

- With an average follow-up of 54 months, patients treated with the addition of cetuximab to radiation therapy had improved outcomes compared to those treated with radiation therapy alone.
- The median duration of time that no cancer recurrences occurred in or near the site of original cancer was 24.4 months for patients treated with cetuximab/radiation therapy, compared to only 14.9 months for those treated with radiation therapy alone.
- The median duration of overall survival was 49 months for those treated with cetuximab/radiation therapy, compared to only 29.3 months for those treated with radiation therapy alone.
- Progression-free survival was significantly improved for patients treated with cetuximab/radiation therapy.
- Rash and reactions at the site of infusion were the most common side effects experienced by patients treated with cetuximab.

NCCN recommends that use of cetuximab not be dependent on EGFR expression of the tumor. This HMSA policy has taken the stance of the NCCN recommendation in spite of the FDA approval labeling for EGFR expressing colorectal tumors. Testing for EGFR expression has not been perfected at this time and patients who may benefit from cetuximab may not be eligible based on this test.

Results from phase II and III clinical trials of the anti-EGFR cetuximab and panitumumab when used either as monotherapy or in combination with chemotherapy have shown that patients with metastatic colorectal carcinoma may benefit from these therapies, and both agents are approved by the US Food and Drug Administration (FDA) for treatment of metastatic colorectal cancer. Stratified analyses of data from these trials by KRAS mutational status not detected (wild type) or abnormal (mutated) indicated that patients with KRAS mutation in codon 12 or 13 did not benefit from treatment with cetuximab or panitumumab.

The American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend that all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR monoclonal antibody therapy should have their tumors tested for KRAS mutations in a CLIA-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR monoclonal antibody therapy as part of their treatment.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

2. Erbitux (cetuximab) full prescribing information. ImClone Systems, Inc., Rev. March 2013
17. NCCN Drugs and Biologics Compendium-Cetuximab 2013.