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Medication Policy Manual | **Policy No:** dru187

Topic: Erbitux®, cetuximab | **Date of Origin:** January 1, 2010

Committee Approval Date: November 10, 2017 | **Next Review Date:** November 2018

Effective Date: December 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Cetuximab (Erbitux) is a monoclonal antibody used to treat specific types of cancer. It is given via intravenous infusion.

Policy/Criteria

I. Most contracts require prior authorization approval of cetuximab (Erbitux) prior to coverage. Cetuximab (Erbitux) may be considered medically necessary when criterion A, or B below is met:

A. A diagnosis of advanced (unresectable) or metastatic colorectal cancer (CRC) when no KRAS mutation is present (for use with KRAS wild type tumors only).

OR

B. A diagnosis of advanced (unresectable), metastatic, or recurrent squamous cell carcinoma of the head and neck (SCCHN).

II. Administration and Authorization Period

A. Regence Pharmacy Services does not consider cetuximab (Erbitux) to be a self-administered medication.

B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Cetuximab (Erbitux) is considered not medically necessary when used for the treatment of metastatic non-small cell lung cancer (NSCLC).

IV. Cetuximab (Erbitux) is considered investigational when used for all other conditions, including but not limited to:

A. Biliary tract cancer
B. Breast cancer
C. Cervical cancer
D. Cutaneous squamous cell carcinoma
D. EGFR-overproducing cancers (other than NSCLC)
E. Esophageal adenocarcinoma
F. Gastric cancer
G. Pancreatic cancer

Position Statement

- Cetuximab (Erbitux), an intravenously administered monoclonal antibody that targets epidermal growth factor receptor (EGFR), has been shown to be safe and effective when used in the treatment of colorectal cancer (CRC), and squamous cell cancer of the head and neck (SCCHN).
- In CRC, mutations in the KRAS protein are associated with resistance to cetuximab (Erbitux). Cetuximab (Erbitux) is only effective in KRAS wild-type CRC (no KRAS mutations are present).

- Although not FDA approved for used in non-small cell lung cancer (NSCLC), cetuximab (Erbitux) has been used in the metastatic disease setting based on a study that reported a nominal (one month) improvement in survival when it was added to front-line chemotherapy. A second study found no difference in survival with cetuximab (Erbitux). Because there are now more effective and better tolerated targeted therapies available for this condition, its use has fallen out of favor. The National Comprehensive Cancer Network (NCCN) NSCLC guideline no longer recommends the use of cetuximab (Erbitux) in NSCLC.
- Cetuximab (Erbitux) is being studied in several other types of cancers that overexpress EGFR. However, the evidence is preliminary and larger studies are needed to establish safety and efficacy of cetuximab (Erbitux) in these cancers.

Clinical efficacy

COLORECTAL CANCER (CRC)

- Several large, randomized controlled trials have studied the efficacy of cetuximab (Erbitux) in CRC in different settings. [6-11] Evidence from the individual studies was unreliable for reasons that included lack of blinding and high proportions of non-completers. However, the trials studied a large number of subjects and response rates were similar across all of the trials which helps support the potential benefit of cetuximab (Erbitux) in CRC.
    * In patients with metastatic CRC who had progression of disease on irinotecan alone, overall tumor response and time to progression of disease was improved in patients receiving a combination of cetuximab (Erbitux) plus irinotecan versus cetuximab (Erbitux) alone. [6]
    * In patients with metastatic CRC who had been previously treated with a fluoropyrimidine, irinotecan and oxaliplatin, monotherapy with cetuximab (Erbitux) improved median overall survival (OS) over best supportive care. The median OS was 6.1 months in the cetuximab (Erbitux) group and 4.6 months in the supportive care group. In a subgroup analysis, only patients with wild-type KRAS benefited from cetuximab (Erbitux) therapy (those with KRAS mutations were resistant). [7, 8]
    * Cetuximab (Erbitux) plus chemotherapy (FOLFIRI) improved progression-free survival (PFS) in patients with CRC who had unresectable metastases. The median PFS was 8.9 months in the FOLFIRI plus cetuximab (Erbitux) group versus 8.0 months in the FOLFIRI alone treatment group. [9]
    * In patients with metastatic CRC, time-to-progression of disease was improved with cetuximab (Erbitux) plus chemotherapy (FOLFOX) versus chemotherapy alone in the subgroup of patients whose tumors did not have KRAS mutations. [10]
    * A large randomized controlled trial comparing first-line irinotecan plus cetuximab (Erbitux) versus irinotecan alone in patients with metastatic CRC demonstrated an improvement in PFS with the combination arm (irinotecan plus cetuximab). [11] There was no difference in OS between the two groups.

- The National Comprehensive Cancer Network (NCCN) guidelines list cetuximab (Erbitux) as an option for unresectable advanced or metastatic CRC when given in combination with FOLFOX, FOLFIRI, or irinotecan, or as monotherapy after failure of irinotecan- and platinum-based regimens when no KRAS/NRAS mutation is present. [2, 3]

SQUAMOUS CELL CANCER OF THE HEAD AND NECK (SCCHN)

- Several poor quality trials studied the use of cetuximab (Erbitux) in the treatment of SCCHN. [1, 12-13] The fact that the trials studied a large number of subjects and reported improvements in a variety of outcomes helps to support the potential benefit of cetuximab (Erbitux) in SCCHN.
    * A randomized controlled trial in 424 patients studied cetuximab (Erbitux) in combination with radiation therapy. Cetuximab (Erbitux) plus radiation therapy improved the median duration of locoregional control of head and neck cancer over use of radiation alone (24.4 months versus 14.9 months, respectively). [12]
    * In a small single arm study in patients with recurrent or metastatic SCCHN who had disease progression within 30-days of a platinum-based therapy, monotherapy with cetuximab (Erbitux) led to an objective tumor response of 13%. [1]
    * In a randomized controlled trial in 442 patients with recurrent of metastatic SCCHN, the addition of cetuximab (Erbitux) to first-line therapy with a platinum plus fluorouracil improved OS over chemotherapy alone. The median OS was 10.1 months in the combination group versus 7.4 months with chemotherapy. [13]
- The NCCN Head and Neck cancer guidelines list cetuximab (Erbitux) as an option for SCCHN when given with radiation or chemotherapy (category 1 recommendation), and as a single agent for recurrent, unresectable or metastatic disease (category 1 recommendation). [4]

NON-SMALL CELL LUNG CANCER

- A large, low quality, open-label trial demonstrated improved OS with cetuximab (Erbitux) in combination with first-line chemotherapy in 1,125 patients with advanced non-small cell lung cancer (NSCLC). [14]
    * Patients all had EGFR-positive tumors.
    * Chemotherapy included a combination of cisplatin and vinorelbine.
    * Patients were excluded from the study if they had known brain metastasis.
    * Overall survival (OS) was 11. 3 months in the cetuximab (Erbitux) plus chemotherapy group and 10.1 months in the chemotherapy group alone. This difference in OS is not likely clinically relevant.
- A subsequent, unreliable, open-label trial performed in 676 patients with advanced or recurrent NSCLC studied the combination of a platinum plus a taxane with and without cetuximab (Erbitux). The addition of cetuximab (Erbitux) to the standard chemotherapy regimen did not improve PFS or OS in this population. [17]

- The NCCN NSCLC guideline no longer recommends cetuximab (Erbitux) for use in metastatic NSCLC because there are now more effective options for use in this condition. [5]

Regence Pharmacy Services performs independent analyses of oncology medications. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN guidelines.

OTHER CANCERS

- Cetuximab (Erbitux) added to conventional chemotherapy did not demonstrate any clinical benefit in patients with advanced pancreatic cancer [15, 18], cervical cancer [19], metastatic adenocarcinoma of the esophagus [20], breast cancer [23], gastric cancer [24], or in NSCLC after failure of prior therapy with erlotinib (Tarceva) or gefitinib (Iressa). [21]
- Several, small, uncontrolled, preliminary studies have been conducted in advanced biliary tract cancer. [22, 25] Larger, controlled studies employing clinical endpoints are needed to confirm potential efficacy.
- A small, open-label, uncontrolled trial evaluated cetuximab (Erbitux) as first-line treatment in patients with unresectable cutaneous squamous cell carcinoma. Larger, controlled studies demonstrating improvements in clinical benefit are needed. [26]
- Several small, unreliable studies have evaluated cetuximab (Erbitux) in various EGFR-expressing tumors. Results are inconclusive. Additional studies of better design are necessary to establish the safety and effectiveness in these patient populations. [16]

Safety

- Cetuximab (Erbitux) package labeling contains boxed warnings for severe infusion reactions, some of which have been fatal, and the potential for cardiopulmonary arrest and/or sudden death. [1]
- Other potentially serious safety concerns with cetuximab (Erbitux) include pulmonary toxicity, severe dermatologic toxicities, and electrolyte abnormalities. [1]
- The most common adverse events reported with cetuximab (Erbitux) include skin rashes, fatigue, abdominal pain, infections, shortness of breath, diarrhea, constipation and vomiting. [1]

Dosing and Administration

- Cetuximab (Erbitux) is given as an intravenous infusion at a rate not to exceed 10 mg/min. [1]
- For non-serious infusion reactions, the rate of infusion should be decreased 50%. [1]
- The dose of cetuximab (Erbitux) should be modified for severe acneform rash. [1]

Cross References
Avastin®, bevacizumab, Medication Policy Manual, Policy No. 215
Keytruda®, pembrolizumab, Medication Policy Manual, Policy No. 367
Stivarga®, regorafenib, Medication Policy Manual, Policy No. 284
Zaltrap®, ziv-aflibercept, Medication Policy Manual, Policy No. 279

Codes	Number	Description
HCPCS	J9055	Injection, cetuximab, 10 mg
ICD-10	C17.0 – C17.2, C17.8, C17.9, C18.0 – C18.9, C78.00 – C78.02, C78.6, C78.7, Z85.038	Colon Cancer
ICD-10	C00.0 – C00.6, C00.8, C00.9, C01, C02.0 – C02.4, C02.8, C02.9, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C05.01, C05.1, C06.0, C06.2, C06.8, C06.89, C06.9, C09.0, C09.1, C09.8, C09.9, C10.3, C11.0 – C11.3, C11.8, C11.9, C12, C13.0 – C13.2, C13.8, C13.9, C14.0, C14.2, C14.8, C31.0, C31.1, C32.0 – C32.3, C32.8, C32.9, C44.0, C44.02, C44.09, C76.0, D37.01, D37.02, D37.05, D37.09, D38.0, D38.5, D38.6, Z85.21, Z85.22, Z85.810, Z85.818, Z85.819	Head and Neck Cancer

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4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 2.2017, Available at: http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf.
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Revision History

Revision Date	Revision Summary
11/10/2017	Added cutaneous squamous cell carcinoma as investigational
9/9/2016	There were no changes to coverage criteria with this annual update.