BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Erbitux® (cetuximab)

Policy #: 656
Category: Pharmacology

Effective Date: February 26, 2018
Latest Review Date: February 24, 2018

Background:
Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Erbitux® (cetuximab) is a recombinant human mouse chimeric monoclonal IgG1 antibody that binds to and inhibits the biologic activity of the human epidermal growth factor receptor (EGFR). It is thought to interfere with the growth of cancer cells by blocking the activation of receptor-associated kinases, inducing apoptosis and decreasing the production of vascular endothelial growth factor production. Antibody-dependent cellular toxicity (ADCC) against specific human tumor types may also be mediated by cetuximab.

Policy:

Effective for dates of service on or after February 26, 2018:

Colorectal and Anal Adenocarcinoma:

Blue Advantage will treat **Erbitux® (cetuximab)** as a **covered benefit** for treatment of individuals with **Stage IV, KRAS wild–type* colon, rectal, colorectal, small bowel, anal adenocarcinoma, or appendiceal adenocarcinoma** when **all** of the following criteria are met:

- The individual has not received prior treatment with panitumumab****** (Vectibix); **AND**
- Erbitux® (cetuximab) is not used in combination with anti-VEGF agents (for example, bevacizumab); **AND**
- Erbitux® **(c**etuximab) may be used for only one line of therapy, **AND**
- Erbitux® **(c**etuximab) is used as a single agent or as part of combination therapy

Head and Neck Cancer:

Blue Advantage will treat **Erbitux (cetuximab)** as a **covered benefit** for the treatment of individuals with **squamous cell cancer of the head and neck** when the following criteria are met:

- The individual has not received prior treatment with panitumumab,****AND**
- Erbitux® (cetuximab) is not used in combination with anti-VEGF agents (for example, bevacizumab); **AND**
- Erbitux® (cetuximab) may be used for only one line of therapy, **AND**
- Erbitux® (cetuximab) is used in **one** of the following indications:
    - In combination with radiation therapy, for the treatment of locally or regionally advanced disease; **or**
    - As a single agent for recurrent or metastatic disease in patients who failed prior platinum-based therapy; **or**
    - As first line therapy for metastatic or recurrent disease in combination with platinum-based chemotherapy with 5-FU (fluorouracil); **or**
    - As a single agent or in combination therapy with or without radiation therapy for any of the following indications:
        - unresectable locoregional recurrence; **or**
        - second primary in individuals who have received prior radiation therapy; **or**
        - resectable locoregional recurrence in individuals who have not received prior radiation therapy; or
        - distant metastases

Squamous Cell Carcinoma of the Skin:

Blue Advantage will treat **erbitux® (cetuximab)** as a **covered benefit** for the treatment of individuals with **unresectable regional recurrence or distant metastatic squamous cell skin carcinoma** when **all** of the following criteria are met:

- The individual has not received prior treatment with panitumumab****AND**
- Erbitux® **(c**etuximab) is not used in combination with anti-VEGF agents (for example, bevacizumab); **AND**
- Erbitux® **(c**etuximab) may be used for only one line of therapy,

Blue Advantage will treat **erbitux® (cetuximab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

***Note**: KRAS wild-type means the gene is normal or lacking mutations
****Note:** A course of panitumumab discontinued because of adverse reaction, not progressive disease, is not considered prior treatment.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Colorectal Adenocarcinoma

Treatment of Metastatic Disease

Cetuximab is currently FDA approved for treatment of EGFR-expressing, metastatic colorectal carcinoma used in combination with irinotecan, in individuals who are refractory to both oxaliplatin- and irinotecan-based regimens and as a single agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma in individuals who are intolerant to irinotecan-based chemotherapy; in combination with radiation therapy. The prescribing information notes that cetuximab is not indicated in Ras-mutant colorectal cancer or in those cases in which the Ras mutation status in unknown. KRAS testing is discussed further below.

The criteria in the Policy Statement are based on the selection criteria in the pivotal trial as well as the expert view of medical practitioners practicing in the clinical area of oncology, and who have familiarity with the available evidence at this time. While both cetuximab and panitumumab are used in the treatment of metastatic colorectal cancer, there are no published head-to-head comparisons between the drugs. Additionally, there are no data, nor is there a compelling rationale to support the use of one of these agents after the therapeutic failure of the other and this practice is not recommended by the National Comprehensive Cancer Network®

(NCCN®). In addition, there is no published peer reviewed literature to support use of cetuximab in second or subsequent lines of therapy when cetuximab was used as initial therapy.

In 2016, the NCCN Clinical Practice Guidelines in Oncology® for advanced stage IV colon and rectal adenocarcinoma include off-label recommendations for cetuximab as a single agent and in combination therapy based on 2A category of evidence and uniform consensus. These guidelines do not recognize the use of cetuximab for treatment of squamous cell anal cancer. In addition, for small bowel adenocarcinoma, the NCCN guideline recommends "Systemic chemotherapy according to the colon cancer guidelines." These recommendations were based on 2A category of evidence and uniform consensus.

There are several recommended off-label uses of cetuximab in combination therapy for metastatic colorectal carcinoma. These regimens include the use of agents such as fluorouracil (5-FU), irinotecan and oxaliplatin. In some situations, the oral formulation of 5-FU, capecitabine, is recommended as equivalent to infused 5-FU.

Cetuximab in Combination with Other Monoclonal Antibodies

In a phase III open-label trial, 732 individuals with metastatic, unresectable colon or rectal carcinoma were randomized to receive treatment with capecitabine-bevacizumab (CB) and oxaliplatin, or capecitabine-bevacizumab-cetuximab (CBC) with oxaliplatin. The CBC cohort had a significantly decreased median progression-free survival (PFS), quality of life and health status compared to the CB group. The authors concluded that the addition of cetuximab to capecitabine, oxaliplatin and bevacizumab "resulted in a significant decrease in progression-free survival and a poorer quality of life."

Adjuvant Therapy

Alberts and colleagues (2012) reported results from a phase III randomized trial investigating the addition of cetuximab to adjuvant chemotherapy for individuals with stage III disease. The trial was halted when data from the second interim analysis did not demonstrate improved disease-free survival (DFS) probabilities in comparison to the control group (74.6% compared to 71.5%) respectively. The investigators noted although cetuximab has demonstrated improved outcomes in the metastatic colorectal setting, additional studies are needed to determine the efficacy of cetuximab in the adjuvant setting.

Adenocarcinomas of the Small Bowel and Appendix

Adenocarcinomas of the small bowel of appendix are rare cancers for which no NCCN Guidelines exist. Localized small bowel adenocarcinomas are treated with surgical resection, but local and distant recurrences are common and optimal perioperative therapy is unknown. Data on treatment of appendiceal adenocarcinomas are also quite limited. Most patients receive debulking surgery with systemic or intraperitoneal therapy. Acknowledging the lack of high-level data, the panel recommends that adenocarcinomas of the small bowel or appendix be treated with systemic chemotherapy according to the 2016 NCCN Guidelines for Colon Cancer.

Anal Cancer

Squamous cell anal cancer is the most common histologic form of anal cancer. Adenocarcinoma and melanoma of the anal canal represent infrequently occurring subtypes of anal carcinoma.

The management of anal adenocarcinoma generally follows management strategies for rectal cancer according to the NCCN Rectal Cancer Clinical Practice Guidelines in Oncology™ (NCCN, 2016). Specialty consensus opinion also supports the recommendations to treat stage IV anal adenocarcinoma similar to stage IV colorectal adenocarcinoma.

KRAS Mutation

Persons with the *KRAS* oncogene mutation do not derive benefit from antiepidermal growth factor (anti-EGFR) therapies like cetuximab or panitumumab. KRAS mutations are associated with reduced overall and progression-free survival as well as increased treatment failure rates among patients with advanced colorectal cancer treated with anti-EGFR antibodies. Therefore, *KRAS* testing must be done prior to initiation of colorectal cancer chemotherapy with these agents.

Studies of metastatic colorectal carcinoma treatment have shown there are subsets of individuals who are not as responsive to anti-EGFR monoclonal antibodies. Research into the KRAS gene has demonstrated that the absence of mutations in the KRAS gene (i.e. KRAS wild-type) is a predictive factor for a positive response to cetuximab therapy. Therefore the mutation status of the KRAS has emerged as an important selection criterion and is included in the FDA label. For example, in a systematic review and meta-analysis, Adelstein and colleagues (2011) analyzed data from eleven studies that included 8,924 individuals treated with anti-EGFR therapy. Individuals with KRAS wild-type had a hazard ratio (HR) for progressive disease of 0.80 (4,436 individuals 95% confidence interval [CI], 0.64, 0.99) compared to 1.11 (3,119 individuals, 95% CI, 0.97, 1.27) in those with the mutant KRAS. The authors concluded the status of KRAS mutation modified the treatment effect of anti-EGFR therapy in the treatment of metastatic CRC. Van Cutsem (2011) reported updated results from a phase III randomized controlled trial (CRYSTAL) of cetuximab combined with irinotecan in first-line therapy for metastatic CRC. The KRAS status was determined in 1,063 (89%) individuals of a total 1,198 participants. In individuals with KRAS wild-type metastatic CRC treated with the cetuximab regimen, there were significant improvements in overall survival (OS) with a median survival of 23.5 months compared to 20.0 months, and improved response rates of 57.3% compared to 39.7% ($p<0.001$) in the control group. The authors concluded KRAS mutation status was a predictive biomarker for efficacy of cetuximab. Other studies have offered similar conclusions.

The 2016 NCCN guidelines include recommendations for KRAS gene testing for all stage IV colon and rectal disease. Use of cetuximab is indicated for individuals with tumors that express the wild-type KRAS gene. The American Society of Clinical Oncology (ASCO) issued a provisional, consensus clinical opinion based on systematic reviews of literature primarily from phase II and III clinical trials involving individuals with metastatic colorectal cancer:

> All individuals with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations in a CLIA-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then individuals with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment.

Unlike KRAS testing, EGFR testing of colorectal tumor cells has not demonstrated predictive value in determining the likelihood of a response to either cetuximab or panitumumab. Thus, this testing is not required to establish medical necessity for this indication for cetuximab. However, in 015, the product label was updated to note the following for colorectal cancer. “Determine the EGFR-expression status using FDA-approved tests prior to initiating.”

Head and Neck Carcinoma
In 2006, the FDA approved cetuximab in combination with radiation therapy, as treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN). An additional approval was given for use as a single agent for the treatment of individuals with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed. In 2011, the FDA approved cetuximab in combination with platinum-based therapy with 5-FU for the first-line treatment of individuals with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck. The FDA based their approval, in part, to the results of randomized Phase III trials reporting that the addition of cetuximab to standard chemotherapy regimens improved response rates and survival.

Since expression of EGFR has been detected in nearly all individuals with head and neck cancer, individuals enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR expression prior to study entry.

Additional recommended off-label uses for cetuximab include single-agent, combination with chemotherapy, with or without radiation therapy for the treatment of recurrent, unresectable or metastatic squamous cell carcinoma of the head and neck.

Squamous Cell Carcinoma of the Skin (SCCS)
The 2016 NCCN guidelines note the rarity of cutaneous squamous cell cancer with distant metastases, and the lack of systemic therapy information. Retrospective case reports have described responses to cetuximab treatment in individuals with metastatic, unresectable SCCS. In a phase II, multicenter, open-label study, cetuximab was used as first-line chemotherapy to treat individuals with metastatic, unresectable SCCS. The initial dose of cetuximab infusion was 400 mg/m^2, with subsequent weekly doses of 250 mg/m^2. The primary endpoint was disease control rate (DCR) after 6 weeks of treatment. Thirty-one participants were evaluable out of 36 enrolled individuals. Based on intent to treat analysis, the DCR was 69% (95% CI, 52% to 84%). The best overall response rate was 28% (95% CI, 14% to 45%) which included 2 individuals with CR and 6 participants with PR. The most frequently occurring adverse event was grade 1 to grade 2 acne-like rash.

The efficacy of cetuximab as a treatment for squamous cell carcinoma was noted in limited but supportive published case series and specialty consensus opinion, including the NCCN Clinical Practice Guideline (2016) category 2A recommendation.

Non-Small Cell Lung Cancer (NSCLC)
The role of cetuximab in NSCLC has been controversial. The key pieces of data are the results of two randomized trials, the open-label FLEX trial and the BMS099 trial, both of which compared cetuximab with and without chemotherapy in individuals with advanced NSCLC.

The FLEX trial randomized 1125 participants to receive chemotherapy (cisplatin, vinorelbine) alone (n=568) or chemotherapy plus cetuximab (n=557). With a median follow-up of 23.8 months, there was a significantly prolonged OS in the chemotherapy plus cetuximab group versus chemotherapy alone (HR 0.871, 0.762 – 0.996; p=0.044). The median OS in the chemotherapy plus cetuximab group was 11.3 months (9.4-12.4) versus 10.1 months (9.1–10.9) in the group treated with chemotherapy.

The BMS099 trial randomized 676 participants to receive chemotherapy (taxane/carboplatin [TC]) alone (n= 338) or chemotherapy plus cetuximab (n=338). There was no significant difference in median progression free survival (4.40 months for cetuximab/TC, 4.24 months for TC alone, p=0.236). The cetuximab/TC group had a slightly longer OS of 9.69 months, but it was not statistically significant versus 8.38 months for the TC group (HR=0.890; 95% CI, 0.754 – 1.051; P=0.169).

The clinical significance of these results has been questioned. In 2009, the American Society of Clinical Oncology (ASCO) clinical guideline update on chemotherapy for stage IV NSCLC, recommendations for first-line chemotherapy included cetuximab with cisplatin and vinorelbine for individuals with EGFR-positive tumors. This guideline was updated in 2011, without any change to the recommendation for use of cetuximab.

Janjigian and colleagues (2014) evaluated the use of afatinib and cetuximab in individuals with advanced EGFR-mutant lung cancer who had been heavily pre-treated and had acquired resistance to erlotinib/gefitinib (n=126). Treatment continued until disease progression, intolerable adverse events withdrawal or death. Efficacy endpoints included objective response (OR) and progression-free survival (PFS). Within the treated population, 29% (37/126) had confirmed OR and of those, 18% (22/126) had at least a 50% shrinkage of the tumor size. The median duration of response lasted 5.7 months. None of the subjects showed a complete response to treatment. An additional 41% (52/126) were reported as having stable disease. The median PFS was 4.7 months (95% CI, 4.3–6.4). Treatment related adverse events (AEs) were reported in 99% of subjects. Grade 3 and 4 AEs were reported in 44% and 2% of the treated population respectively. Serious treatment related events were reported in 14% of individuals and 13% of individuals discontinued treatment due to treatment related AEs.

The 2016 NCCN guideline for NSCLC has added a 2A recommendation for the use of afatinib/cetuximab for those with sensitizing EGFR mutations who have progressed following EGFR tyrosine kinase inhibitors (TKIs) and chemotherapy. This was based on one phase Ib, open-label, uncontrolled, multicenter study. Confirmatory trials are underway. In 2015, NCCN assigned a category 3 recommendation (i.e., denoting significant disagreement that the intervention is appropriate) for the use of cetuximab in the treatment of advanced NSCLC citing concerns of toxicity with the regimen containing cetuximab, cisplatin and vinorelbine. This regimen was removed from the treatment algorithms and recommended chemotherapy lists. The guidelines concluded, "Some clinicians feel that although the FLEX trial results were statistically significant they were not clinically significant."

In 2013, the American College of Chest Physicians (ACCP) published guidelines regarding the treatment of Stage IV NSCLC which assigned a 2B recommendation to cetuximab regimens and suggested that the drug should not be used outside of a clinical trial. The document summarizes the data as follows:

In summary, the data are conflicting with regard to the impact of adding cetuximab to platinum-based chemotherapy in the first-line setting of advanced NSCLC. There appears to be an improvement in response rates as a result of adding cetuximab, but no effect on PFS and no consistent effect on overall survival. In the trials in which there has been a survival benefit, the magnitude of the benefit is very modest and not felt to be clinically robust, particularly relative to the toxicity.

Key Words:

Metastatic colorectal cancer (CRC), KRAS mutation analysis, monoclonal antibody, human epidermal growth factor receptor (EGFR), head and neck cancer, non-small cell lung cancer, appendiceal adenocarcinoma, anal adenocarcinoma, cetuximab, Erbitux, squamous cell carcinoma of the skin (SCCS)

Approved by Governing Bodies:

On February 12, 2004, the U.S. FDA approved the Biologics License Application (BLA) for cetuximab for metastatic colorectal cancer.

On March 1, 2006, the FDA approved cetuximab for use in combination with radiation therapy for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck or as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom platinum-based therapy has failed.

On November 7, 2011, the FDA approved cetuximab in combination with platinum-based therapy plus 5-FU for the first-line treatment of patients with recurrent locoregional disease and/or metastatic squamous cell carcinoma of the head and neck (SCCHN).

On July 6, 2012, the FDA approved Erbitux in combination with FOLFIRI (irinotecan, 5-FU, leucovorin) for first-line treatment of colorectal cancer.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

HCPCS:

J9055 Injection, cetuximab 10 mg

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Policy History:

Adopted for Blue Advantage, February 2018
Available for comment February 26 through April 11, 2018

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.