Policy Retired
Effective September 1, 2014
Refer to Article (A48896) 'Chemotherapeutic Agents'

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:
Cetuximab, Erbitux®

Policy #: 371
Category: Pharmacology
Latest Review Date: October 2012
Policy Grade: B

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:

Cetuximab (Erbitux®; ImClone, Branchburg, NJ) 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 September 1, 2014:
Policy replaced by chemotherapeutic agents (A48896) Provider page.

Effective for dates of service on or after September 2, 2011 through September 1, 2014:
Blue Advantage will treat **cetuximab** as a **covered** benefit for the treatment of **EGFR-expressing metastatic colorectal cancer** when KRAS gene mutation testing is documented and the tumor is determined to be KRAS wild-type and one of the following criteria is met:

- As monotherapy in patients who are intolerant to irinotecan-based chemotherapy; **OR**
- As monotherapy in patients who failed both irinotecan- and oxaliplatin-based regimens; **OR**
- In combination with irinotecan, in patients refractory to irinotecan-based chemotherapy; **OR**
- As first line therapy in combination with irinotecan, 5-fluorouracil and folinic acid (leucovorin); **OR**
- As first line therapy in combination with oxaliplatin, 5-fluorouracil, and leucovorin; **OR**
- In combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen.

NOTE: KRAS mutation analysis is required prior to treatment of EGFR-expressing metastatic colorectal cancer whether cetuximab is used in combination therapy or as a single agent.

OR

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

- In combination with radiation therapy for locally or regionally advanced disease.
- As monotherapy for recurrent or metastatic disease in patients who failed prior platinum-based therapy.
- As combination therapy for metastatic or recurrent disease in patients refractory to platinum-based therapy; **OR**
- As first line therapy for metastatic or recurrent disease in combination with platinum-based chemotherapy.

OR

Blue Advantage will treat **cetuximab** as a **covered** benefit for the treatment of advanced or metastatic **non-small cell lung cancer**.

In addition, the following criteria **must** be met to treat any of the above diseases:

- The patient has not received prior treatment with panitumumab; **AND**
- Cetuximab is not used in combination with other monoclonal antibodies; **AND**
- ~~If Cetuximab is used as initial therapy, it would not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage if used in second or subsequent lines of therapy.~~

Dosage and frequency of administration should be based on the product label or one of the standard referenced compendia. The medial record should contain the patient's height, weight, etc. to determine the dosage.

Effective for dates of service on or after April 15, 2010 and before September 2, 2011:
For the initial course of treatment with this drug:

Blue Advantage will treat **cetuximab** as a **covered** benefit for the treatment of **EGFR-expressing metastatic colorectal cancer** when KRAS gene mutation testing is documented and the tumor is determined to be KRAS wild-type and one of the following criteria is met:

- As monotherapy in patients who are intolerant to irinotecan-based chemotherapy; **OR**
- As monotherapy in patients who failed both irinotecan- and oxaliplatin-based regimens; **OR**
- In combination with irinotecan, in patients refractory to irinotecan-based chemotherapy; **OR**
- As first line therapy in combination with irinotecan, 5-fluorouracil and folinic acid; **AND**

NOTE: KRAS mutation analysis is required prior to treatment of EGFR-expressing metastatic colorectal cancer whether cetuximab is used in combination therapy or as a single agent.

OR

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

- In combination with radiation therapy for locally or regionally advanced disease.
- As monotherapy for recurrent or metastatic disease in patients who failed prior platinum-based therapy.
- As combination therapy for metastatic or recurrent disease in patients refractory to platinum-based therapy.

OR

Blue Advantage will treat **cetuximab** as a **covered** benefit for the treatment of advanced or metastatic **non-small cell lung cancer**.

In addition, the following criteria **must** be met to treat any of the above diseases:

- The patient has not received prior treatment with panitumumab; **AND**
- Cetuximab is not used in combination with other monoclonal antibodies
- ~~If Cetuximab is used as initial therapy, it would not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage if used in second or subsequent lines of therapy.~~

Dosage and frequency of administration should be based on the product label or one of the standard referenced compendia. The medial record should contain the patient's height, weight, etc. to determine the dosage.

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:

This medical criterion for coverage is based on the FDA-labeled indications and/or compendia based accepted off-label indications and /or the National Comprehensive Cancer Network (NCCN) drug compendium.

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

Approved by Governing Bodies:

In February 2004, the U.S. FDA approved the Biologics License Application (BLA) for cetuximab for metastatic colorectal cancer.
In March 2006, the U.S. FDA approved the BLA for cetuximab for squamous cell carcinoma of the head and neck.
July 2012, US FDA approved Erbitux in combination with FOLFIRI (irinotecan, 5-FU, leucovorin) for 1st line treatment for colon cancer.

Benefit Application:

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

Current Coding:

81275 KRAS (v-Ki-RAS2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis, variants in codons 12 and 13

81403 Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) – includes *KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene)*(e.g. carcinoma) gene analysis, variants on exon 3 (e.g. codon 61) **(effective 1/1/13)**

81405 Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) – includes KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) (e.g., Noonan syndrome), full gene sequence **(effective 1/1/13)**

88363 Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)

HCPCS Code:

J9055 Injection, cetuximab 10 mg

Previous Coding:

S3713 KRAS mutation analysis testing **(Deleted effective April 1, 2012)**

There are no specific CPT codes for KRAS mutation analysis. Multiple codes describing genetic analysis could likely be used (e.g., codes from 83890-83912 and 88363). **(Deleted effective 1/1/13)**

References:

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2. Bokemeyer C, et al. KRAS status and efficacy of first-line treatment in patients with metastatic CRC with FOLFOX with or without cetuximab: The OPUS experience. Journal Clinical Oncology 2008; 26 (May 20 suppl: Abstract 4000).
3. Bonner J, et al. Radiotherapy plus cetuximab for squamous cell carcinoma of the head and neck. NEJM 2006; 354; 567-578.
4. Cervantes A, et al. Correlation of KRAS status (wild type [wt] vs. mutant [mt]) with efficacy to first-line cetuximab in a study of cetuximab single agent followed by cetuximab + FOLFIRI in patients with metastatic CRC. Journal Clinical Oncology 2008; 26 (May 20 Suppl; Abstract 4129).

5. Cetuximab Drug Point Summary. Micromedex® Healthcare Series. Drugdex Drug Point, www.thomsonhc.com.
6. Cunningham D, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. NEJM 2004; 351: 337-345.
7. DeRooch W, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Annals of Oncology, March 2008; 19(3): 508-515.
8. Jean GW, et al. Epidermal growth factor receptor monoclonal antibodies for the treatment of metastatic colorectal cancer. Pharmacotherapy, June 2008; 28(6): 742-754.
9. Jonker DJ, et al. Cetuximab for the treatment of colorectal cancer. NEJM, November 2007; 357(20): 2040-2048.
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13. Messersmith WA, et al. Targeting EGFR in CRC. NEJM 2008; 359(17): 1834-1836.
14. National Comprehensive Cancer Network (NCCN). NCCN Drugs & Biologics Compendium™ - Cetuximab. http://www.nccn.org.
15. Van Cutsen E, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic CRC treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. Clinical Oncology 2008; 26 (May 20 Suppl: Abstract 2).
16. Zhu Z, et al. Targeted cancer therapies based on antibodies directed against EGFR: Status and perspectives. Acta Pharmacology Sin 2007; 28(9): 1476-1493.

Policy History:

Adopted for Blue Advantage, August 2009
Available for comment August 12-September 25, 2009
Available for comment February 23-April 8, 2010
Medical Policy Group, December 2010, Code update
Medical Policy Group, August 2011; Updated Policy section
Medical Policy Administration Committee, September 2011
Available for comment September 2 through October 17, 2011
Medical Policy Group, December 2011
Medical Policy Group, February 2012
Medical Policy Group, August 2012
Medical Policy Group, October 2012
Medical Policy Group, January 2013
Medical Policy Group, September 2014

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.