Name of Policy: Cetuximab, Erbitux®

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

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
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 for dates of service on or after September 2, 2011
Cetuximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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

Cetuximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of **squamous cell cancer of the head and neck** when any of the following criteria are met:

- In combination with radiation therapy for locally or regionally advanced disease; or
- As monotherapy for recurrent or metastatic disease in patients who failed prior platinum-based therapy; or
- 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
Cetuximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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 medical record should contain the patient’s height, weight, etc. to determine the dosage.

Effective for dates of service prior to September 2, 2011:
For the initial course of treatment with this drug, Cetuximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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;

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

Cetuximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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; or
- As monotherapy for recurrent or metastatic disease in patients who failed prior platinum-based therapy; or
- As combination therapy for metastatic or recurrent disease in patients refractory to platinum-based therapy.

OR
Cetuximab meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage 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 medical record should contain the patient’s height, weight, etc. to determine the dosage.

Blue Cross and Blue Shield of Alabama 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 Cross and Blue Shield of Alabama administers benefits based on the members’ contract and corporate 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.
ITS: Home Policy provisions apply
FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.
Lowe’s Precertification Requirement—Effective for dates of service on or after February 1, 2010
please contact Care Continuum at 866-240-4734 or fax the prescription with accompanying clinical information to 877-540-6223 for precertification. (This Blue Cross and Blue Shield of Alabama’s medical policy does not apply for Lowe’s members for dates of service on or after February 1, 2010. This policy was in effect for Lowe’s prior to February 1, 2010).
Pre-certification requirements: Not applicable

Current Coding:
CPT codes:

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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>81275</td>
<td>KRAS (v-Ki-RAS2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis, variants in codons 12 and 13</td>
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<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of &gt;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)</td>
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<td>81405</td>
<td>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)</td>
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<tr>
<td>88363</td>
<td>Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)</td>
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HCPCS:

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<td>J9055</td>
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Previous Coding:

HCPCS:

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<tr>
<td>S3713</td>
<td>KRAS mutation analysis testing (deleted 04/01/2012)</td>
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References:


Policy History:
Medical Policy Group, July 2009 (3)
Medical Policy Administration Committee, August 2009
Available for comment August 10-September 23, 2009
Medical Policy Administration Committee, February 2010
Available for comment February 18-April 7, 2010
Medical Policy Group, December 2010 (1); Coding update, effective January 1, 2011, added 88363
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 (3): Coding update effective January 2012-added code 81275 and deleted S3173
Medical Policy Group, August 2012 (3): Updated Policy section by adding folic acid drug name “leucovorin” & Approved by Governing Bodies by adding new FDA label information
Medical Policy Group, October 2012 (1) Updated Policy section by removing wording “For the initial course of treatment with this drug” and the criteria point “If Cetuximab is used as initial therapy, it would not meet medical criteria for coverage if used in second or subsequent lines of therapy.”
Medical Policy Administration Committee, October 2012
Medical Policy Group, January 2013 (1) Update to Coding with addition of codes 81403 and 81405 related to KRAS testing; no change in policy statement

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.