Epidermal Growth Factor Receptor (EGFR) Antagonist Drugs

Policy Number: 2014D0025I  
Effective Date: 6/1/2014

Related Medical or Drug Policies:  
Oncology Medication Clinical Coverage Policy

Related Coverage Determination Guidelines:  
None

INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

Please refer to the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium for updated information on oncology indications for cetuximab or panitumumab. This policy will continue to be updated for KRAS/NRAS testing requirements. For related information, please refer to the Oncology Medication Clinical Coverage Policy.

Treatment with cetuximab (Erbitux®) or panitumumab (Vectibix®) is unproven for colorectal cancer or other solid tumors when used in persons with the KRAS or NRAS oncogene mutation.5,6

Persons without the KRAS/NRAS wild type oncogene do not demonstrate improved survival with anti-epidermal growth factor receptor (anti-EGFR) agents.

EGFR Antagonists Policy: Drug Policy (Effective 06/01/2014)

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It is theorized that cetuximab and panitumumab do not target EGFR receptors associated with these specific KRAS mutations and thus are unable to block their activation. EGFR signal transduction results in KRAS wild-type activation whereas cells with KRAS mutations appear to be unaffected by EGFR inhibition.

Centers for Medicare and Medicaid Services (CMS):
Medicare does have a National Coverage Determination (NCD) for cetuximab. Refer to the NCD for Anti-Cancer Chemotherapy for Colorectal Cancer (110.17). Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Cetuximab (Erbitux®).

Medicare does not specifically have a National Coverage Determination (NCD) for panitumumab (Vectibix). However there is an NCD that mentions chemotherapy for colorectal cancer. Refer to the NCD for Anti-Cancer Chemotherapy for Colorectal Cancer (110.17). Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Chemotherapy Drugs and their Adjuncts and K-ras Testing Required before Epidermal Growth Factor Receptor Antibody Use in Colorectal Cancer (L31766).

Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf. (Accessed February 5, 2014)

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

BACKGROUND

Epidermal Growth Factor Receptor (EGFR) Testing

Epidermal growth factor receptor (EGFR) belongs to the erbB family of receptors, which includes EGFR (HER1/erbB1), erbB2 (HER2/neu), erbB3 (HER3) and erbB4 (HER4). EGFR plays a key role in a number of cellular processes including proliferation, regeneration, differentiation and development. EGFR is found in tissues of epithelial, neuronal and mesenchymal origin. EGFR is stimulated by a number of substrates results in the activation of tyrosine kinases leading to an intracellular signal cascade and cellular response.¹

EGFR is highly expressed in a number of solid tumors including colorectal, breast, head and neck, non-small cell lung, ovarian and prostate cancers. Overexpression of EGFR has been correlated with disease progression, resistance to therapy and a poor outcome. Blockade of EGFR has been shown to inhibit tumor growth and enhances the activity of other chemotherapeutic agents and radiotherapy.¹⁴ The antitumor effects of EGFR blockade can be EGFR Antagonists Policy: Drug Policy (Effective 06/01/2014)

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attributed to the arrest of cell cycle progression, induction of apoptosis and inhibition of angiogenesis.2,4

Persons with the KRAS or NRAS 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. NRAS mutations are significantly associated with lower disease control rate and response rate to anti-EGFR therapies. Therefore, KRAS and NRAS testing must be done prior to initiation of colorectal cancer chemotherapy with these agents. If KRAS mutation in codon 12 or 13 or NRAS mutation is detected, then patients with colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment.5-8,11

CLINICAL EVIDENCE

Professional Societies

The 2014 National Comprehensive Cancer Network (NCCN) Colon Cancer and Rectal Cancer Guidelines provide recommendations for use of cetuximab and panitumumab in colon and rectal cancers.

There is sufficient evidence demonstrating that mutations in codons 12 and 13 of exon 2 of the KRAS genes predict lack of response to the EGFR inhibitors such as cetuximab. Additionally, more recent literature shows mutations in KRAS outside of exon 2 and mutations in NRAS are also predictive for a lack of response. It is not recommended to treat patients with a known KRAS (exon 2 or non-exon 2) or NRAS mutation-positive disease with cetuximab, either alone or as part of a chemotherapy combination regimen, as there is virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guideline that NCCN recommendations involving cetuximab relate specifically to patients with disease characterized by the KRAS/NRAS wild-type genes only.

It is recommended that gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing. A specific testing methodology is not recommended.5,6

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Erbitux (cetuximab) is approved by the FDA for treatment of:

1. Head and Neck Cancer4
   • Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy,
   • Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil (5-FU),
   • Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.
2. Colorectal Cancer4 [KRAS mutation-negative (wild-type), EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved tests]
   • In combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first-line treatment,
   • As a single agent, in those patients who have failed irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan,
   • In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy.
Erbitux is not an effective treatment for patients with colorectal cancer that harbor somatic mutations in codons 12 and 13 (exon 2). Erbitux is not indicated for treatment of KRAS mutation-positive colorectal cancer.\(^4\)

Vectibix is approved by the FDA as a single agent for the treatment of metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens.\(^5\)

- Approval is based on progression-free survival; no data demonstrate an improvement in disease-related symptoms or increased survival with Vectibix.
- Vectibix is not indicated for the treatment of patients with KRAS mutation-positive mCRC or for whom KRAS mCRC status is unknown.

### APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J9055</td>
<td>Injection, cetuximab, 10 mg</td>
</tr>
<tr>
<td>J9303</td>
<td>Injection, panitumumab, 10 mg</td>
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### REFERENCES


### POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>6/1/2014</td>
<td>Policy updated per annual review. Added panitumumab to drug policy and renamed policy to Epidermal Growth Factor Receptor (EGFR) Antagonist Drugs. Updated coverage criteria to include NRAS testing. Approved by the National Pharmacy &amp; Therapeutics Committee 4/8/2014. Policy 2013D0025H archived.</td>
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<tr>
<td>12/9/2008</td>
<td>Policy revised with changes in background, coverage rationale, clinical recommendations, and clinical precautions sections.</td>
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<tr>
<td>10/21/2005</td>
<td>HCPCS code J9055 added to Coding Section per direction from the Reimbursement Medical Policy Operations Manager.</td>
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