

**Medication Policy Manual**

**Policy No:** dru187

**Topic:** Erbitux<sup>®</sup>, cetuximab

**Date of Origin:** September 11, 2009

**Revised Date:** September 11, 2009

**Next Review Date:** September 2010

**Effective Date:** February 1, 2010

**IMPORTANT REMINDER**

This Medical 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 medical policy is to provide a guide to coverage. Medical 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 colorectal cancer and head and neck cancer.

## **Policy/Criteria**

**I.** Most contracts require prior authorization approval of cetuximab prior to coverage. Cetuximab may be considered medically necessary when criterion A, B or C 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).

**OR**

**C.** A diagnosis of advanced (stage IIIb or IV) non-small cell lung cancer when criteria 1, 2, 3, and 4 below are met:

1. Documentation is provided that the tumor expresses epidermal growth factor receptor (EGFR).

**AND**

2. Cetuximab is given in conjunction with a platin (e.g. cisplatin or carboplatin) and vinorelbine.

**AND**

3. The patient has not had prior chemotherapy.

**AND**

4. There is no known brain metastasis.

**II.** Administration and Authorization Period

**A.** Regence does not consider cetuximab 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 is considered investigational when used for all other conditions, including but not limited to:
- A.** EGFR-overproducing cancers
  - B.** Pancreatic cancer

## **Position Statement**

### *Summary*

- Cetuximab is a monoclonal antibody that targets epidermal growth factor receptor (EGFR). By binding to EGFR, cetuximab blocks specific protein signals which stop the growth of cancer cells. <sup>[1]</sup>
- Cetuximab is used to treat colorectal cancer (CRC), squamous cell cancer of the head and neck (SCCHN), and non-small cell lung cancer (NSCLC). <sup>[2-5]</sup> However, mutations in a specific protein, the KRAS protein, are associated with resistance to cetuximab. For example, cetuximab therapy is not effective in colorectal cancer where KRAS mutations occur. <sup>[1]</sup>
- Cetuximab is being studied in other types of cancers that express EGFR. However, the evidence is preliminary and larger studies are needed to establish safety and efficacy of cetuximab in these cancers.

### *Clinical efficacy*

#### **COLORECTAL CANCER**

- Several large, randomized controlled trials have studied the efficacy of cetuximab in colorectal cancer (CRC) in different settings. <sup>[6-11]</sup> 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 to support the potential benefit of cetuximab 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 plus irinotecan versus cetuximab alone. <sup>[6]</sup>

- \* In patients with metastatic CRC who had been previously treated with a fluoropyrimidine, irinotecan and oxaliplatin, monotherapy with cetuximab improved median overall survival over best supportive care. The median survival was 6.1 months in the cetuximab group and 4.6 months in the supportive care group. In a subgroup analysis, only patients with wild-type KRAS benefited from cetuximab therapy (those with KRAS mutations were resistant). <sup>[7, 8]</sup>
- \* Cetuximab plus chemotherapy (FOLFIRI) improved progression-free survival in patients with colorectal cancer who had unresectable metastases. Median progression-free survival times were 8.9 months in the FOLFIRI plus cetuximab group versus 8.0 months in the FOLFIRI alone treatment group. <sup>[9]</sup>
- \* In patients with metastatic colorectal cancer, time-to-progression of disease was improved with cetuximab plus chemotherapy (FOLFOX) versus chemotherapy alone in the subgroup of patients whose tumors did not have KRAS mutations. <sup>[10]</sup>
- \* A large randomized controlled trial comparing first-line irinotecan plus cetuximab versus irinotecan alone in patients with metastatic CRC demonstrated an improvement in progression-free survival with the combination arm (irinotecan plus cetuximab). <sup>[11]</sup> There was no difference in overall survival between the two groups.
- The National Comprehensive Cancer Network guidelines list cetuximab as an option for advanced or metastatic colon cancer when given in combination with FOLFOX or FOLFIRI, or as monotherapy after failure of irinotecan- and platin-based regimens when no KRAS mutations are present. <sup>[2, 3]</sup>

## SQUAMOUS CELL CANCER OF THE HEAD AND NECK

- Several unreliable trials studied the use of cetuximab in the treatment of head and neck cancer. <sup>[1, 12-13]</sup> 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 in head and neck cancer.
- \* A randomized controlled trial in 424 patients studied cetuximab in combination with radiation therapy. Cetuximab 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). <sup>[12]</sup>

- \* In a small single arm study in patients with recurrent or metastatic squamous cell cancer of the head and neck who had disease progression within 30-days of a platin-based therapy, monotherapy with cetuximab led to an objective tumor response of 13%. <sup>[1]</sup>
- \* In a randomized controlled trial in 442 patients with recurrent or metastatic squamous cell cancer of the head and neck, the addition of cetuximab to first-line therapy with a platin plus fluorouracil improved overall survival over chemotherapy alone. The median overall survival was 10.1 months in the combination group versus 7.4 months with chemotherapy. <sup>[13]</sup>
- The National Comprehensive Cancer Network guidelines list cetuximab as an option for squamous cell cancer of the head and neck when given with radiation or chemotherapy, and as a single agent for recurrent, unresectable or metastatic disease. <sup>[4]</sup>

#### NON-SMALL CELL LUNG CANCER

- A large, unreliable, open-label trial demonstrated improved overall survival with cetuximab in combination with first-line chemotherapy in 1,125 patients with advanced non-small cell lung cancer. <sup>[14]</sup>
  - \* 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 was 11.3 months in the cetuximab plus chemotherapy group and 10.1 months in the chemotherapy group alone.
- The National Comprehensive Cancer guidelines list cetuximab as a first-line option for EGFR-positive non-small cell lung cancer when given in combination with cisplatin plus vinorelbine in patients who do not have documented brain metastasis. <sup>[5]</sup>

## OTHER CANCERS

- Cetuximab added to conventional chemotherapy did not demonstrate any clinical benefit in patients with advanced pancreatic cancer in a small randomized controlled trial. <sup>[15]</sup>
- Several small, unreliable studies have evaluated cetuximab in EGFR-expressing tumors. Results are inconclusive. Additional studies of better design are necessary to establish the safety and effectiveness in these patient populations. <sup>[16]</sup>

### *Safety*

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

### *Dosing and Administration*

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

## References

1. Erbitux<sup>®</sup> (cetuximab) Prescribing Information. ImClone Systems, Inc.; Branchburg, NJ; July 2009.
2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Colon Cancer. Version 3.2009, Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/colon.pdf](http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf). Accessed on 8/31/09.

3. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 3.2009, Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/rectal.pdf](http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf). Accessed on 8/31/09.
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 1.2009, Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/head-and-neck.pdf](http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf). Accessed on 8/31/09.
5. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2.2009, Available at: [http://www.nccn.org/professionals/physician\\_gls/PDF/nscl.pdf](http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf). Accessed on 8/31/09.
6. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337-45.
7. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcborg JR, Tu D, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007;357(20):2040-8.
8. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359(17):1757-65.
9. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360(14):1408-17.
10. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2009;27(5):663-71.
11. Sobrero AF, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26(14):2311-9.
12. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354(6):567-78.

13. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008; 359(11):1116-27.
14. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, et al.; FLEX Study Team. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet.* 2009;373(9674):1525-31.
15. Cascinu S, Berardi R, Labianca R, Siena S, Falcone A, et al.; Italian Group for the Study of Digestive Tract Cancer (GISCAD). Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial. *Lancet Oncol.* 2008;9(1):39-44.
16. Micromedex<sup>®</sup> Healthcare Series [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated Periodically.

<b>Cross References</b>
n/a

<b>Codes</b>	<b>Number</b>	<b>Description</b>
HCPCS	J9055	Injection, cetuximab, 10 mg