Vectibix® (Panitumumab) Granted Approval for Expanded Indications in the European Union

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THOUSAND OAKS, Calif., Nov. 15, 2011 /PRNewswire via COMTEX/ --

Amgen (NASDAQ: AMGN) today announced that the European Commission (EC) has approved a variation to the marketing authorization for Vectibix® (panitumumab) to include indications for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC) in first-line in combination with FOLFOX and in second-line in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). This approval of Vectibix applies to all 27 European Union (EU) member states. Prior to this approval, Vectibix had received conditional approval in the EU as monotherapy. The monotherapy indication was also further revised to state that Vectibix is indicated for the treatment of patients with wild-type *KRAS* mCRC as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Colorectal cancer is the second most common cancer in women worldwide and the third most common cancer in men. Approximately 1.2 million cases of colorectal cancer are expected to occur globally. With more than 630,000 deaths worldwide per year, it is the third leading cause of cancer-related death in the Western world. The highest incidence rates are found in Japan, North America, parts of Europe, New Zealand, and Australia, and rates are low in Africa and Southeast Asia.(1)

"Colorectal cancer can have a devastating impact on the lives of patients affected by this disease," said Professor Jean-Yves Douillard, director of Clinical and Translational Research, ICO Centre R Gauducheau, France. "This European Commission approval for Vectibix earlier in the treatment continuum marks a welcome and important addition of treatment choice in an area where few targeted agents have shown to be effective when used with chemotherapy."

Data from studies 20050203 (PRIME) and 20050181 ('181) showed that adding Vectibix to either FOLFOX or FOLFIRI chemotherapy improved progression-free survival (PFS) versus chemotherapy alone for patients with wild-type *KRAS* mCRC. Additionally, the overall response rate (ORR) of Vectibix plus chemotherapy was higher than chemotherapy alone. Although numerically greater, the improvement in median overall survival (OS) did not achieve statistical significance in the Vectibix arm of either trial.(2)(3) The Amgen PRIME and '181 studies were among the first Phase 3 studies to prospectively analyze the effect of an anti-epidermal growth factor receptor (EGFR) inhibitor based on *KRAS* status in patients with mCRC.

Adverse events in the PRIME and '181 studies included known toxicities associated with EGFR therapy, such as rash, diarrhea, and hypomagnesemia. The incidence of grade 3/4 infusion reactions in the treatment arms for the two trials was approximately one percent. In patients with mutated *KRAS* tumors, outcomes were inferior for those receiving Vectibix plus FOLFOX versus FOLFOX alone. Vectibix should only be used in those patients in whom wild-type *KRAS* status has been confirmed.

"Today's decision by the EC to extend the therapeutic indications for Vectibix marks a promising step forward for those patients facing an aggressive disease where limited treatment options are available," said Willard H. Dere, M.D., senior vice president and international chief medical officer at Amgen. "This is a significant milestone for Amgen and highlights our commitment to deliver medicines that make a real difference to the lives of patients."

Vectibix is already approved and established in more than 40 countries as a monotherapy treatment for patients with wild-type *KRAS* mCRC, when standard chemotherapy is no longer effective. In the United States (U.S.), Vectibix received accelerated approval in September 2006 as a monotherapy for the treatment of patients with EGFR-expressing mCRC after disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The use of Vectibix is not recommended in patients whose tumors have *KRAS* mutations in codon 12 or 13. In Russia, Japan and Israel, Vectibix is also approved for use in combination with chemotherapy for patients with wild-type *KRAS* mCRC.

About *KRAS*

Results from studies performed over the last 25 years indicate that *KRAS* plays an important role in cell growth regulation. In mCRC, EGFR transmits signals through a set of intracellular proteins. Upon reaching the nucleus, these signals instruct the cancer cell to reproduce and metastasize, leading to cancer progression.(4) Anti-EGFR antibody therapies work by inhibiting the activation of EGFR, thereby inhibiting downstream events that lead to malignant signaling. However, in patients whose tumors harbor a mutated *KRAS* gene, the *KRAS* protein is always turned "on," regardless of whether the EGFR has been activated or therapeutically inhibited. *KRAS* mutations occur in approximately 40 to 50 percent of mCRC patients.(5)(6)

About Vectibix

Vectibix is the first fully human anti-EGFR antibody approved by the U.S. Food and Drug Administration (FDA) for the treatment of mCRC. Vectibix was approved in the U.S. in September 2006 as a single agent for the treatment of patients with EGFR-expressing mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The effectiveness of Vectibix as a single agent for the treatment of EGFR-expressing mCRC is based on PFS. More than half of patients who receive Vectibix monotherapy respond to treatment with an average six month PFS benefit. Currently no data are available that demonstrate an improvement in disease-related symptoms or increased survival with Vectibix.

Retrospective subset analyses of mCRC trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of mCRC with these mutations.(7)

Important U.S. Product Safety Information (Monotherapy)

WARNING: DERMATOLOGIC TOXICITY and INFUSION REACTIONS

Dermatologic Toxicity: Dermatologic toxicities occurred in 89 percent of patients and were severe (NCI-CTC grade 3 or higher) in 12 percent of patients receiving Vectibix monotherapy. [See Dosage and Administration (2.1), Warnings and Precautions (5.1), and Adverse Reactions

(6.1)].

Infusion Reactions: Severe infusion reactions occurred in approximately one percent of patients. Fatal infusion reactions occurred in postmarketing experience [See Dosage and Administration (2.1), Warnings and Precautions (5.2), and Adverse Reactions (6.1, 6.3)].

The most common adverse events of Vectibix are skin rash with variable presentations, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea, including diarrhea resulting in dehydration.

Important European Product Safety Information

- Vectibix has been approved in the European Union for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC):
  - in first-line in combination with FOLFOX
  - in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan)
  - as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.
- Vectibix is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to the product and in patients with interstitial pneumonitis or pulmonary fibrosis. Vectibix should not be administered in combination with oxaliplatin-containing chemotherapy to mCRC patients with mutant *KRAS* tumors or for whom *KRAS* tumor status is unknown.
- Adverse events of special importance associated with Vectibix and/or EGFR monoclonal antibody therapies include dermatologic-related reactions, pulmonary complications, electrolyte disturbances, infusion-related reactions (including rare reports with fatal outcome) and ocular toxicities. Acute renal failure has been observed in patients who develop severe diarrhea and dehydration. These events should be monitored carefully, see Summary of Product Characteristics for information on appropriate management of these adverse events.
- Vectibix should not be used in combination with IFL chemotherapy or in combination with bevacizumab containing chemotherapy. For patients with ECOG 2 performance status, assessment of benefit-risk is recommended prior to initiation of Vectibix in combination with chemotherapy for treatment of mCRC.

About Amgen

Amgen discovers, develops, manufactures and delivers innovative human therapeutics. A biotechnology pioneer since 1980, Amgen was one of the first companies to realize the new science's promise by bringing safe and effective medicines from lab, to manufacturing plant, to patient. Amgen therapeutics have changed the practice of medicine, helping millions of people around the world in the fight against cancer, kidney disease, rheumatoid arthritis, bone disease and other serious illnesses. With a deep and broad pipeline of potential new medicines, Amgen remains committed to advancing science to dramatically improve people's lives. To learn more about our pioneering science and our vital medicines, visit www.amgen.com.

Forward-Looking Statements

This news release contains forward-looking statements that are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission (SEC) reports filed by Amgen, including Amgen's most recent annual report on Form 10-K and most recent periodic reports on Form 10- Q and Form 8-K. Please refer to Amgen's most recent Forms 10-K, 10-Q and 8-K for additional information on the uncertainties and risk factors related to our business. Unless otherwise noted, Amgen is providing this information as of November 15, 2011 and expressly disclaims any duty to update information contained in this news release.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products after they are on the market. Our business may be impacted by government investigations, litigation and products liability claims. We depend on third parties for a significant portion of our manufacturing capacity for the supply of certain of our current and future products and limits on supply may constrain sales of certain of our current products and product candidate development.

In addition, sales of our products are affected by the reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment as well as U.S. legislation affecting pharmaceutical pricing and reimbursement. Government and others' regulations and reimbursement policies may affect the development, usage and pricing of our products. In addition, we compete with other companies with respect to some of our marketed products as well as for the discovery and development of new products. We believe that some of our newer products, product candidates or new indications for existing products, may face competition when and as they are approved and marketed. Our

products may compete against products that have lower prices, established reimbursement, superior performance, are easier to administer, or that are otherwise competitive with our products. In addition, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors and there can be no guarantee of our ability to obtain or maintain patent protection for our products or product candidates. We cannot guarantee that we will be able to produce commercially successful products or maintain the commercial success of our existing products. Our stock price may be affected by actual or perceived market opportunity, competitive position, and success or failure of our products or product candidates. Further, the discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations.

The scientific information discussed in this news release relating to new indications for our products is preliminary and investigative and is not part of the labeling approved by the U.S. FDA, European Medicines Agency (EMA) or similar regulatory bodies for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses. Only the FDA, EMA or similar regulatory bodies can determine whether the products are safe and effective for these uses. Healthcare professionals should refer to and rely upon the approved labeling for the products, and not the information discussed in this news release.

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(3) Peeters, M et al. Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second-Line Treatment in Patients With Metastatic Colorectal Cancer. *J Clin Oncol* 28, 2010.

(4) Malumbres, M. and Barbacid, M. RAS oncogenes: the first 30 years. *Nature Reviews Cancer*. 3:459-65, 2003

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(6) Friday BB and Adjei AA. K-ras as a target for cancer therapy. Biochim. Biophys. Acta 1756: 127-144, 2005

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