



FDA Approves ERBITUX[®] (cetuximab) for First-Line Recurrent Locoregional or Metastatic Head and Neck Cancer in Combination with Platinum-based Chemotherapy with 5-Fluorouracil

- **ERBITUX Now Approved for Five Indications Across Two Tumor Types**
- **ERBITUX Plus Platinum-Based Chemotherapy with 5-Fluorouracil (CT) is the First Regimen Approved in 30 Years with Extended Overall Survival in Patients with Recurrent Locoregional or Metastatic Squamous Cell Carcinoma of the Head and Neck**
- **Combination with CT Significantly Improved Median Overall Survival and Progression-Free Survival versus CT Alone by 36 Percent and 67 Percent, Respectively**

(New York and Indianapolis, November 7, 2011) - [Eli Lilly and Company](#) (NYSE: LLY) and [Bristol-Myers Squibb Company](#) (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved ERBITUX[®] (cetuximab), in combination with platinum-based chemotherapy with 5-fluorouracil (CT), for the first-line treatment of recurrent locoregional or metastatic squamous cell carcinoma of the head and neck (SCCHN). The approval, which is based on data from the landmark EXTREME (ERbituX in first-line Treatment of REcurrent or MEtastatic head & neck cancer) trial, makes ERBITUX plus CT the first treatment regimen approved in 30 years with extended overall survival in patients with recurrent locoregional or metastatic SCCHN.

EXTREME, which was previously published in the *New England Journal of Medicine*, was a Phase 3 open label, randomized, multicenter, controlled trial. This study was conducted outside the U.S. by Merck KGaA, Darmstadt, Germany, and used European Union (EU)-approved cetuximab. ERBITUX provides approximately 22% higher exposure relative to the EU-approved cetuximab used in the EXTREME trial; these pharmacokinetic data, together with the results of the EXTREME trial and other clinical trial data establish the efficacy of ERBITUX at the recommended dose. EXTREME showed that cetuximab plus CT in the first-line treatment of recurrent locoregional or metastatic SCCHN resulted in superior efficacy across clinically meaningful endpoints, including overall survival, progression-free survival, and objective response rate compared to CT. Cetuximab plus CT significantly extended patients' median overall survival by 36% compared to patients who received CT alone (10.1 months vs. 7.4 months, respectively) [HR: 0.80; 95% CI: 0.64-0.98; p=0.034]. Cetuximab plus CT also significantly increased median progression-free survival by 67% (5.5 vs. 3.3 months, respectively) [HR: 0.57; 95% CI: 0.46-0.72; p<0.0001] compared to CT alone. A significant improvement in objective response rate was also demonstrated (36% vs. 20%, odds ratio, 2.33 [95% CI: 1.50-3.60]; p=0.0001).

The full Prescribing Information for ERBITUX includes a boxed warning regarding infusion reactions and cardiopulmonary arrest. Serious infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients in clinical trials, with fatal outcome reported in less than 1 in 1000. Healthcare providers should immediately interrupt and permanently discontinue ERBITUX infusion for serious infusion reactions. Cardiopulmonary arrest and/or sudden death occurred in 2% of patients with squamous cell carcinoma of the head and neck treated in a clinical trial with ERBITUX and radiation therapy and in 3% of patients with squamous cell carcinoma of the head and neck treated with EU-approved cetuximab in combination with platinum-based therapy with 5-fluorouracil (5-FU) in the EXTREME trial. Healthcare providers should closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX administration.

Selected adverse events of any grade occurring in at least 10% of patients receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU or platinum-based therapy with 5-FU alone were: acneiform rash (70% vs 2%, respectively), nausea (54% vs 47%), infection (44% vs 27%), rash (28% vs 2%), diarrhea (26% vs 16%), anorexia (25% vs 14%), pyrexia (22% vs 13%), acne (22% vs 0), dermatitis acneiform (15% vs 0), dry skin (14% vs <1%), alopecia (12% vs 7%), hypokalemia (12% vs 7%), hypocalcemia (12% vs 5%), hypomagnesemia (11% vs 5%), infusion reaction (10% vs <1%), and conjunctivitis (10% vs 0). Since U.S.-licensed ERBITUX provides approximately 22% higher exposure relative to the EU-approved cetuximab, the data provided above may underestimate the incidence and severity of adverse reactions anticipated with ERBITUX for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX.

Please see Important Safety Information including Boxed WARNINGS on pages 6-9.

"With the improvements seen across objective response rates, progression free survival, and overall survival, this trial establishes ERBITUX plus CT as an important advancement in the treatment of first-line recurrent or metastatic SCCHN," said Jan Vermorken, MD, PhD., Professor Emeritus at the University of Antwerp and primary investigator on the EXTREME trial. "Today's approval is important for patients with SCCHN because ERBITUX is the only biologic agent with a proven overall survival benefit in combination with CT in recurrent or metastatic disease."

The EXTREME regimen is the only Category 1 recommendation for combination therapy in the professional treatment guidelines for Head and Neck Cancer from the National Comprehensive Cancer Network[®] (NCCN[®]) for the indication of recurrent, unresectable, or metastatic disease (non-nasopharyngeal) that is incurable. **

This is the fifth indication approved for ERBITUX and the third indication demonstrating overall survival. ERBITUX was previously approved for the initial treatment of locally or regionally advanced SCCHN in combination with radiation therapy. This approval was based on data from a randomized clinical trial (N=424) where ERBITUX administered at the recommended dose in combination with radiation therapy increased median locoregional control (24.4 vs 14.9 months with radiation alone; P=0.005; HR: 0.68 [95% CI: 0.52-0.89]) and median overall survival (49.0 vs 29.3 months with radiation alone; P=0.03; HR: 0.74 [95% CI: 0.57-0.97]). ERBITUX, as a single agent, is indicated for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed. At that time, the FDA noted that ERBITUX was the first drug approved for head and neck cancer since the 1950's. ERBITUX remains the first and only monoclonal antibody to be approved by the FDA for this type of cancer.

ERBITUX is FDA approved in colorectal cancer (CRC) as a single agent for the treatment of EGFR-expressing metastatic CRC after failure of both irinotecan- and oxaliplatin-based regimens. This approval was based upon data from a randomized clinical trial (N=572) where ERBITUX administered at the recommended dose in combination with best supportive care (BSC) resulted in median overall survival of 6.14 months vs. 4.57 months with BSC alone (hazard ratio, 0.77; 95% confidence interval, 0.64-0.92; p=0.0046). ERBITUX as a single agent is also indicated for the treatment of EGFR-expressing metastatic CRC in patients who are intolerant to irinotecan-based regimens. ERBITUX, in combination with irinotecan, is indicated for the treatment of EGFR-expressing metastatic CRC in patients who are refractory to irinotecan-based chemotherapy. The effectiveness of ERBITUX in combination with irinotecan is based on objective response rates. The U.S. Prescribing Information further states that no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX in combination with irinotecan for the treatment of EGFR-expressing metastatic colorectal carcinoma. Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for ERBITUX in patients whose tumors had *K-ras* mutations in codon 12 or 13. Use of ERBITUX is not recommended for the treatment of colorectal cancer with these mutations.

Since its first approval in 2004, ERBITUX has more than seven years of experience in medical practice. Additionally, approximately 127,000 patients received ERBITUX therapy over that time period in the U.S. alone.

About EXTREME

The approval is based on a Phase 3, open-label, multicenter, randomized study of 442 patients with recurrent or metastatic SCCHN who did not receive prior CT. This study was conducted outside the U.S. by Merck KGaA, Darmstadt, Germany, and used EU-approved cetuximab. Erbitux provides approximately 22% higher exposure relative to the EU-approved cetuximab used in the EXTREME study; these pharmacokinetic data, together with the results of the EXTREME study and other clinical trial data establish the efficacy of ERBITUX at the recommended dose. Patients in this trial, patients were randomized to receive either cetuximab along with a CT (cisplatin or carboplatin and 5-fluorouracil; n=222), or chemotherapy alone (n=220). CT was administered every three weeks for up to 6 cycles, while cetuximab was continued until disease progression or unacceptable toxicity.

The primary endpoint of the pivotal Phase 3 study was overall survival. Secondary efficacy endpoints included progression-free survival and objective response rate.

About Head and Neck Cancer

In 2011, it is estimated that more than 50,000 Americans will develop cancer of the head and neck, including cancers of the tongue, the rest of the mouth, the salivary glands and inside the throat, the voice box and the lymph nodes in the upper neck. Head and neck cancer most often affects people over the age of 50, and men are more than twice as likely to be diagnosed as women. The most common risk factors are tobacco, excessive alcohol use, and HPV infection of the oral cavity.

About ERBITUX[®] (Cetuximab)

ERBITUX (cetuximab) is a monoclonal antibody (IgG1 Mab) designed to inhibit the function of a molecular structure expressed on the surface of normal and tumor cells called the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1). *In vitro* assays and *in vivo* animal studies have shown that binding of ERBITUX to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in induction of apoptosis (cell death), inhibition of cell growth, and decreased matrix metalloproteinase and vascular endothelial growth factor production. *In vitro*, ERBITUX can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that ERBITUX inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of ERBITUX were observed in human tumor xenografts lacking EGFR expression.

INDICATIONS

Head and Neck Cancer

- ERBITUX[®] (cetuximab), in combination with radiation therapy, is indicated for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck
- ERBITUX is indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck.
- ERBITUX, as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed

Colorectal Cancer

- ERBITUX, as a single agent, is indicated for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. ERBITUX, as a single agent, is also indicated for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens
- ERBITUX, in combination with irinotecan, is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. The effectiveness of ERBITUX in combination with irinotecan is based on objective response rates. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX in combination with irinotecan for the treatment of EGFR-expressing metastatic colorectal carcinoma
- Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for ERBITUX in patients whose tumors had K-ras mutations in codon 12 or 13. Use of ERBITUX is not recommended for the treatment of colorectal cancer with these mutations

IMPORTANT SAFETY INFORMATION INCLUDING BOXED WARNINGS

Infusion Reactions

- **Grade 3/4 infusion reactions occurred in approximately 3% of patients receiving ERBITUX[®] (cetuximab) in clinical trials, with fatal outcome reported in less than 1 in 1000**
 - **Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of ERBITUX, included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest**
 - **Immediately interrupt and permanently discontinue ERBITUX infusions for serious infusion reactions**
- **Most (90%) of the severe infusion reactions were associated with the first infusion of ERBITUX despite premedication with antihistamines**
 - **Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion reaction during later infusions**
 - **Monitor patients for 1 hour following ERBITUX infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Longer observation periods may be required in patients who require treatment for infusion reactions**

Cardiopulmonary Arrest

- **Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients with squamous cell carcinoma of the head and neck treated with radiation therapy and ERBITUX, as compared to none of 212 patients treated with radiation therapy alone. In three patients with prior history of coronary artery disease, death occurred 27, 32, and 43 days after the last dose of ERBITUX. One patient with no prior history of coronary artery disease died one day after the last dose of ERBITUX. Fatal cardiac disorders and/or sudden death occurred in 7 (3%) of the 219 patients with squamous cell carcinoma of the head and neck treated with platinum-based therapy with 5-fluorouracil (FU) and European Union (EU)-approved cetuximab as compared to 4 (2%) of the 215 patients treated with chemotherapy alone.**
 - **Carefully consider the use of ERBITUX in combination with radiation therapy or platinum-based therapy with 5-FU in head and neck cancer patients with a history of coronary artery disease, congestive heart failure or arrhythmias in light of these risks**
 - **Closely monitor serum electrolytes including serum magnesium, potassium, and calcium during and after ERBITUX therapy**

Pulmonary Toxicity

- Interstitial lung disease (ILD), which was fatal in one case, occurred in 4 of 1570 (<0.5%) patients receiving ERBITUX in clinical trials. Interrupt ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD

Dermatologic Toxicities

- In clinical studies of ERBITUX, dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, infectious sequelae (eg, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, cheilitis), and hypertrichosis, occurred in patients receiving ERBITUX therapy. Acneiform rash occurred in 76-88% of 1373 patients receiving ERBITUX in clinical trials. Severe acneiform rash occurred in 1-17% of patients
 - Acneiform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days
 - Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae
 - Sun exposure may exacerbate these effects

ERBITUX Plus Radiation Therapy and Cisplatin

- The safety of ERBITUX in combination with radiation therapy and cisplatin has not been established
 - Death and serious cardiotoxicity were observed in a single-arm trial with ERBITUX, radiation therapy, and cisplatin (100 mg/m²) in patients with locally advanced squamous cell carcinoma of the head and neck
 - Two of 21 patients died, one as a result of pneumonia and one of an unknown cause
 - Four patients discontinued treatment due to adverse events. Two of these discontinuations were due to cardiac events

Electrolyte Depletion

- Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX and was severe (NCI CTC grades 3 & 4) in 6-17%. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of ERBITUX therapy. In the squamous cell carcinoma of the head and neck study in combination with platinum-based therapy there was an increased incidence of hypomagnesemia in subjects who received concomitant EU-approved cetuximab and cisplatin therapy with 5-FU compared to cisplatin with 5-FU alone. In contrast, the incidences of hypomagnesemia were similar for those who received cetuximab, carboplatin, and 5-FU compared to carboplatin and 5-FU.
 - Monitor patients periodically for hypomagnesemia, hypocalcemia and hypokalemia, during, and for at least 8 weeks following the completion of, ERBITUX therapy
 - Replete electrolytes as necessary

Late Radiation Toxicities

- The overall incidence of late radiation toxicities (any grade) was higher with ERBITUX in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65%/56%), larynx (52%/36%), subcutaneous tissue (49%/45%), mucous membranes (48%/39%), esophagus (44%/35%), and skin (42%/33%) in the ERBITUX and radiation versus radiation alone arms, respectively
 - The incidence of grade 3 or 4 late radiation toxicities were similar between the radiation therapy alone and the ERBITUX plus radiation therapy arms

Pregnancy and Nursing

- In women of childbearing potential, appropriate contraceptive measures must be used during treatment with ERBITUX and for 6 months following the last dose of ERBITUX. ERBITUX may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. ERBITUX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus
- It is not known whether ERBITUX is secreted in human milk. IgG antibodies, such as ERBITUX, can be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ERBITUX, a decision should be made whether to discontinue nursing or to discontinue ERBITUX, taking into account the importance of ERBITUX to the mother. If nursing is interrupted, based on the mean half-life of cetuximab, nursing should not be resumed earlier than 60 days following the last dose of ERBITUX

Adverse Events

- The most **serious adverse reactions** associated with ERBITUX across all studies were infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus
- The most common adverse reactions associated with ERBITUX (incidence 25%) are cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection

- The most frequent adverse events seen in patients with carcinomas of the head and neck receiving ERBITUX in combination with radiation therapy (n=208) versus radiation alone (n=212) (incidence ≥50%) were acneiform rash (87%/10%), radiation dermatitis (86%/90%), weight loss (84%/72%), and asthenia (56%/49%). The most common grade 3/4 adverse events for ERBITUX in combination with radiation therapy (≥10%) vs radiation alone included: radiation dermatitis (23%/18%), acneiform rash (17%/1%), and weight loss (11%/7%)
- Selected grade 1-4 adverse events occurring in at least 10% of patients with carcinomas of the head and neck receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU or platinum-based therapy with 5-FU alone were: acneiform rash (70% vs 2%, respectively), nausea (54% vs 47%), infection (44% vs 27%), rash (28% vs 2%), diarrhea (26% vs 16%), anorexia (25% vs 14%), pyrexia (22% vs 13%), acne (22% vs 0), dermatitis acneiform (15% vs 0), dry skin (14% vs <1%), alopecia (12% vs 7%), hypokalemia (12% vs 7%), hypocalcemia (12% vs 5%), hypomagnesemia (11% vs 5%), infusion reaction (10% vs <1%), and conjunctivitis (10% vs 0). Since U.S.-licensed Erbitux provides approximately 22% higher exposure relative to the EU-approved cetuximab, the data provided above may underestimate the incidence and severity of adverse reactions anticipated with Erbitux for this indication. However, the tolerability of the recommended dose is supported by safety data from additional studies of Erbitux
- The most frequent adverse events seen in patients with metastatic colorectal cancer (n=288) in the ERBITUX + best supportive care arm (incidence ≥50%) were fatigue (89%), rash/desquamation (89%), abdominal pain (59%), and pain-other (51%). The most common grade 3/4 adverse events (≥10%) included: fatigue (33%), pain-other (16%), dyspnea (16%), abdominal pain (14%), infection without neutropenia (13%), rash/desquamation (12%), and other-gastrointestinal (10%)
- The most frequent adverse events seen in patients with metastatic colorectal cancer (n=354) treated with ERBITUX plus irinotecan in clinical trials (incidence ≥50%) were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common grade 3/4 adverse events (≥10%) included: diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%)

Please see Important Safety Information and [U.S. Full Prescribing Information](#) including **Boxed WARNINGS regarding infusion reactions and cardiopulmonary arrest.**

About ERBITUX Patient Programs

Bristol-Myers Squibb and Lilly are committed to supporting patient access to ERBITUX and have put in place a number of programs to help patients and providers. Destination Access™, which is a Reimbursement Support Program, helps patient access by providing benefits investigation support, prior authorization assistance, appeals assistance and patient assistance. More information about our patient assistance program can be obtained by calling 1-800-861-0048.

In addition to Destination Access, The ERBITUX PATIENT SUPPORT PROGRAM has been developed to provide patients and healthcare providers with information and helpful resources on dermatological toxicities associated with ERBITUX and guidance on how to manage them. For additional information, visit www.erbitux.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

About Bristol-Myers Squibb

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit www.bms.com, or follow us on Twitter at <http://twitter.com/bmsnews>.

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding product development. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. Among other risks, there can be no guarantee that the supplemental application will be approved. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's and Lilly's businesses, particularly those identified in the cautionary statement and risk factors discussion in Bristol-Myers Squibb's and Lilly's Annual Reports on Form 10-K, in their Quarterly Reports on Form 10-Q and their Current Reports on Form 8-K. Neither Bristol-Myers Squibb nor Lilly undertakes any obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

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*Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

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