**Pharmaceutical-Approval Update: Oncology**

Marvin M. Goldenberg, PhD, RPh, MS

---

**Cetuximab (Erbitux™) for IV Use Only**

**Manufacturer:** Imclone Systems, Inc./Bristol-Myers Squibb

**Drug Class:** Recombinant, human/mouse chimeric monoclonal antibody

**Description:** Cetuximab binds specifically to the extracellular domain of human epidermal growth factor receptor (EGFR). Produced in mammalian (murine myeloma) cell culture, cetuximab is composed of the fragment variable (Fv) regions of a murine anti-EGFR antibody with human immunoglobulin G1 (IgG1) heavy and kappa light-chain constant regions. Cetuximab binds to EGFR (HER1, c-ERB-1) on both normal and tumor cells and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands (i.e., transforming growth factor-α, TGFR-α). The binding of cetuximab to EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibited cell growth, induced apoptosis, and decreased production of matrix metalloproteinase and vascular EGF.

EGFR, a transmembrane glycoprotein, is a member of the subfamily of type-1 receptor tyrosine kinases, including EGFR (HER1), HER2, HER3, and HER4. It is constitutively expressed in many normal epithelial tissues, such as the skin and hair follicles. Overexpression of EGFR is also detected in many human cancers, including those of the colon and rectum. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that overexpress EGFR. The addition of cetuximab to irinotecan (Camptosar®, Tirgan), another chemotherapeutic agent for colorectal cancer, or to irinotecan plus 5-fluorouracil (5-FU) in animal studies increased antitumor activity compared with chemotherapy alone.

**Indication:** In combination with irinotecan, cetuximab is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma that is refractory to irinotecan-based chemotherapy. As a single agent, it is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are intolerant of irinotecan chemotherapy. There has been no clinical evidence linking improvement in disease-related symptoms or increased survival with cetuximab.

**Pharmacology:** The efficacy and safety of cetuximab alone or in combination with irinotecan were studied in a randomized, controlled trial with 329 patients and in combination with irinotecan in 138 patients. All of the patients received both drugs. Cetuximab was further evaluated as a single agent in a third clinical trial involving 57 patients. Safety data from an additional 111 patients who received only cetuximab were also evaluated. All of the trials included patients with EGFR-expressing metastatic colorectal cancer whose disease had progressed after irinotecan therapy.

For patients with tumors expressing EGFR and who no longer responded to treatment with irinotecan alone or combined with other chemotherapy drugs, the cetuximab/irinotecan combination shrank tumors in 22.9% of patients and delayed tumor growth by approximately 4.1 months. For patients who received cetuximab alone, the tumor response rate was 10.8% and tumor growth was delayed by 1.5 months.

**Black-Box Warning**

**Infusion Reactions.** Severe infusion reactions occurred in approximately 3% of patients, with rare fatal outcomes (fewer than 1 per 1,000 patients); approximately 90% of these reactions were associated with the first cetuximab infusion. These severe reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, or hoarseness), urticaria, and hypotension. If a severe reaction occurs, the infusion must be interrupted immediately and discontinued permanently.

**Warnings**

**Pulmonary Toxicity.** Interstitial lung disease was reported in three of 663 (fewer than 0.5%) patients with advanced colorectal cancer who were receiving cetuximab. Interstitial pneumonitis with noncardiogenic pulmonary edema resulting in death was reported in one case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while they were receiving cetuximab/irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer who received cetuximab and cisplatin (Platinol®, Bristol-Myers Squibb). In all reported cases, symptoms began to appear between the fourth and 11th doses of treatment.

In the event of acute onset or worsening pulmonary symptoms, cetuximab should be discontinued. If interstitial lung disease is confirmed, cetuximab should be discontinued and appropriate treatment should be instituted.

**Dermatological Toxicity.** In cynomolgus monkeys, cetuximab affected the skin when administered at 0.4 to 4 times the weekly exposure; reactions included inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passages, esophagus, and tongue were similarly affected, and degenerative changes occurred in the renal tubular epithelium. Beginning at about 13 weeks of treatment, 50% of the animals receiving the highest dose died of sepsis.

In clinical studies, dermatological toxicities included acneiform rash, skin drying and fissuring, and inflammatory and infectious sequelae (blepharitis, cheilitis, cellulitis, and cysts). In patients with advanced colorectal cancer, acneiform rash was reported in 88% of all treated patients and was severe (grade 3 or 4) in 12% of these patients.

*Staphylococcus aureus*-based sepsis and abscesses occurred following the development of severe dermatological toxicities. Patients with rashes should be monitored for the development continued on page 171
of inflammation or infection, and these symptoms should be treated promptly.

**Precautions:** Patients must undergo testing for the presence of EGFR expression. The Food and Drug Administration (FDA) has approved a test kit (Dako Cytomation California, Inc.) for analyzing a colon tissue sample. The kit enables the physician to detect a protein (HER1) in the body that stimulates cancerous tissue cell growth. The presence of this protein indicates that a patient is eligible for colon cancer treatment with cetuximab.

**Drug Interactions:** There is no pharmacokinetic interaction between cetuximab in combination with irinotecan.

**Immunogenicity:** Potential immunogenic responses to cetuximab must be evaluated in each patient because of the proteinaceous nature of the biological agent.

**Conclusion:** Cetuximab is the first monoclonal antibody approved for patients with advanced colorectal cancer that has spread to other parts of the body. It is indicated as an IV treatment for cancer and other serious or life-threatening diseases based on early evidence of a product’s effectiveness. Although cetuximab did not extend patients’ lives, it did shrink tumors in some patients and delay tumor growth, especially when used as a combination treatment.

**Source:** Cetuximab prescribing information, Bristol-Myers Squibb. Available at: www.bms.com/landing/data. February 13, 2004.

**Pemetrexed for Injection (Alimta®)**

**Manufacturer:** Eli Lilly

**Drug Class:** Antifolate antineoplastic agent

**Description:** Pemetrexed for injection exerts its action by disrupting folate-dependent metabolic processes that are essential for cell replication. By inhibiting dihydrofolate reductase, thymidylate synthase, and glycaminide ribonucleotide formyl transferase, it interrupts the de novo synthesis of both purines and pyrimidines. As a single agent, it is active against a variety of solid tumors.

**Indication:** In combination with cisplatin, pemetrexed is indicated for patients with unresectable malignant pleural mesothelioma or who are otherwise not candidates for curative surgery. Malignant mesotheliomas are aggressive neoplasms that arise from the surface serosal cells of the pleural, peritoneal, and pericardial cavities.

Pemetrexed 500 mg/m² is administered as an intravenous (IV) infusion over 10 minutes on the first day of each 21-day cycle. Cisplatin 75 mg/m² is infused over two hours, beginning approximately 30 minutes after the pemetrexed injection.

**Pharmacology:** The effectiveness of pemetrexed was established in a clinical trial that compared it in combination with cisplatin and with cisplatin alone. The multicenter, randomized, single-blind study included 448 chemotherapy-naïve patients with malignant pleural mesothelioma. Patients receiving pemetrexed and cisplatin lived three months longer after randomization than did patients who were given cisplatin alone (12 vs. 9 months). Lung function (i.e., forced vital capacity) also improved in the pemetrexed/cisplatin arm compared with the control arm. Pemetrexed must be administered with vitamin B₁₂ and folic acid supplementation to decrease the incidence and severity of adverse drug events (ADEs).

**Warnings**

**Decreased Renal Function.** This product is primarily eliminated unchanged by renal excretion. No dosage adjustment is needed in patients with creatinine clearance of 45 ml/minute or greater. Because insufficient numbers of patients have been studied with creatinine clearance below 45 ml/minute to recommend the appropriate dose, pemetrexed should not be administered when the creatinine clearance is below 45 ml/minute.

**Bone Marrow Suppression.** Pemetrexed can suppress bone marrow function, resulting in manifestations of neutropenia, thrombocytopenia, and anemia. Myelosuppression is usually the dose-limiting toxicity. Dose reductions for subsequent cycles are based on the nadir absolute neutrophil count, the platelet count, and the maximum nonhematologic toxicity seen in the previous cycle.

**Folate and Vitamin B₁₂ Supplementation.** Patients receiving pemetrexed must be instructed to take folic acid and vitamin B₁₂ as a prophylactic measure to reduce treatment-related hematological and gastrointestinal toxicities (e.g., neutropenia, febrile neutropenia, and infections).

**Pregnancy Category D.** This agent may cause fetal harm during pregnancy, although no studies have been conducted in pregnant women. When given to mice on gestation days six through 15, the agent was fetotoxic and teratogenic, causing fetal malformations and cleft palate. Embryotoxicity was characterized by increased embryo fetal deaths and reduced litter sizes.

**Precautions:** The product should be administered under the supervision of a qualified physician with experience in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are available.

Skin rashes have been reported more frequently in patients who are not taking corticosteroids in clinical trials. In patients with clinically significant third-space fluid, practitioners should consider draining the effusion before prescribing pemetrexed. Complete blood counts, including platelet counts and periodic chemistry profiles should be assessed for all patients receiving this product. Patients should be monitored for nadir and recovery values before each dose on days eight and 15 of each cycle, and they should not begin a new cycle of treatment unless the absolute neutrophil count is 1,500 cells/mm³ or higher, the platelet count is 100,000 cells/mm³ or higher, and the creatinine clearance is 45 ml/minute or greater.

Practitioners should use caution when administering ibuprofen with pemetrexed for injection in patients with mild to moderate renal insufficiency. If concomitant administration of a nonsteroidal anti-inflammatory drug (NSAID) is necessary, patients should be monitored closely for renal and gastrointestinal toxicity and especially for myelosuppression.

**Conclusion:** Although asbestos exposure has been established as the primary cause of malignant pleural mesothelioma, there is a long latency period of 30 to 45 years between...
exposure and development of the disease. Shipyard, insulation, and construction workers and asbestos miners and manufacturers seem to be at highest risk. The male-to-female ratio is approximately 4:1. The disease affects between 10,000 and 15,000 people worldwide each year, and this figure is increasing. Most people learn that they have it only after the disease has progressed to an advanced stage, when treatment with surgery or radiation is not possible.

When given with cisplatin, pemetrexed is the first and only chemotherapy FDA-approved drug approved for the treatment of this malignancy when surgery is not an option.


**Oxaliplatin for Injection (Eloxatin™)**

**Manufacturer:** Sanofi-Synthelabo, Inc.

**Drug Class:** Platinum antineoplastic agent

**Description:** Oxaliplatin for injection is an organoplatinum complex in which the platinum atom is joined with 1,2-diaminocyclohexane (DACH) and with an oxalate ligand as a “leaving group,” an atom (or group of atoms) that is displaced as stable species and takes the bonding electrons with it. Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both interstrand and intrastrand platinum–DNA cross-links are formed. These cross-links inhibit DNA replication and transcription. Cytotoxicity is nonspecific for the cell cycle.

**Indication:** Used in combination with infusional 5-fluorouracil/leucovorin (5-FU/LV), oxaliplatin is indicated for treating metastatic carcinoma of the colon or rectum that has recurred or progressed during or within six months after completion of first-line combination therapy with bolus 5-FU/LV and irinotecan (Camptosar®).

**Pharmacology:** A multicenter, randomized, three-arm controlled study was conducted in the U.S. and Canada to compare the efficacy and safety of oxaliplatin in combination with infusional 5-FU/LV at the same dose and 5-FU/LV alone and with single-agent oxaliplatin in patients with advanced colorectal cancer with relapsing or progressive disease during or within six months of first-line combination therapy with bolus 5-FU/LV and irinotecan (Camptosar®).

Oxaliplatin may cause hypersensitivity and anaphylactic or anaphylactoid reactions. These allergic reactions (e.g., rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension) were similar in nature and severity to those reported with other platinum-containing compounds. They occur within minutes of administration and should be managed with appropriate supportive therapy. Drug-related deaths associated with platinum compounds from this reaction have been reported.

**Pregnancy Category D.** Oxaliplatin may cause fetal harm in pregnant women, and women of childbearing age should be advised to avoid becoming pregnant during treatment.

**Precautions**

**Neuropathy.** There have been reports of an early-onset, acute, reversible, primarily peripheral sensory neuropathy that occurs within hours or one to two days of dosing and resolves within 14 days and that may recur with further dosing. A persistent, primarily peripheral sensory neuropathy, lasting more than 14 days, has been characterized by paresthesias, dysesthesias, and hypoesthesias along with deficits in proprioception that interfere with daily activities (e.g., writing, buttoning clothes, swallowing, and difficulty in walking).

**Pulmonary Toxicity.** The product has been associated with pulmonary fibrosis (in 0.7% of study patients), which is sometimes fatal.

**Adverse Drug Effects.** The most frequently reported ADEs with oxaliplatin/infusional 5-FU/LV are acute neuropathy (56%), persistent neuropathy (48%), fatigue (68%), diarrhea (67%), nausea (65%), and vomiting (40%). Hematologic changes include anemia (81%), leukopenia (76%), neutropenia (73%), and thrombocytopenia (64%).

**Conclusion:** Oxaliplatin is used in combination with infusional 5-FU and leucovorin to treat advanced colorectal cancer in patients with recurrent or worsening disease after initial therapy with irinotecan plus bolus 5-FU/LV. Compared with the standard treatment (irinotecan plus 5-FU/LCV), the oxaliplatin/5-FU/LV regimen was superior in terms of prolonging survival, in shrinking tumors in some patients, and in delaying tumor regrowth.