CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125084/S-030

Trade Name: Erbitux

Generic Name: cetuximab

Sponsor: Imclone Systems, Incorporated

Approval Date: September 1, 2005

Indications: To revise the WARNINGS and DOSAGE AND ADMINISTRATION sections of the package insert to include information on infusion observation periods and to revise the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert to provide information on hypomagnesemia.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084/S-030

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125084/30

SEP 01 2005

ImClone Systems, Incorporated
Attention: Nikhil Mehta, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
33 ImClone Drive
Branchburg, NJ 08876

Dear Dr. Mehta:

Your request to supplement your biologics license application for Cetuximab to revise the WARNINGS and DOSAGE AND ADMINISTRATION sections of the package insert to include information on infusion observation periods and to revise the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert to provide information on hypomagnesemia has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

This information will be included in your biologics license application file.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachment: Revised Labeling

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
Summary Text: Clinical Supplmt. – Labeling Only
REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:

- **Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).**

RIS Data Check:

- **Verify short summary – Ltr. & Submission screen should match.**
- **Check Letter for PMCs (if PMCs – add "PMCs – Approved With" special characteristic code.)**
- **Perform Review Completion Process**
- **Milestone: Confirm Approved Status**

cc: HFD-107/P. Keegan
HFD-107/L. Pai-Scherf
HFD-109/S. Sickafuse
HFD-42/C. Broadnax
HFD-430/R. Pratt
HFD-106/K. Weiss
HFD-106/G. Jones
HFM-110/RIMS/R. Eastep
HFD-400/ODS M. Dempsey
HFD-006/Exec sec V. Kinsey
HFD-013/FOI H. Brubaker
HFD-240/OTCOM/ B. Poole
HFD-230/OTCOM/CDER WebMaster
HFD-42/DDMAC/M. Kiester
HFD-410/ODS/DSRCS/ Karen Young
HFD-328/TFRB Blue File/Mike Smedley
HFD-410/CDER Medwatch Safety Labeling
HFD-430/ODS/DDRE (hard copy)
DBOP BLA file (hard copy)

History: Sickafuse:8-4-05: K. Townsend: 8.9.2005:sks:8-15-05

File Name: (S:Sickafuse\Cetuximab\labeling supplements\125084_30\approval letter.doc)

Division	Name/Signature	Date
DBOP	Sickafuse	8-15-05
OODP/DBOP	Karen D. Jones	8-17-05
OODP/DBOP	Patricia Keegan	9-1-05
OOTSP/DBOP	Kelly Covington	9-2-05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084/S-030

LABELING

Rx only

ERBITUX®

(Cetuximab)

For intravenous use only.

WARNING

Infusion Reactions: Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension (see **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions require immediate interruption of the ERBITUX infusion and permanent discontinuation from further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

DESCRIPTION

ERBITUX® (Cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). ERBITUX is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. ERBITUX is produced in mammalian (murine myeloma) cell culture.

ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

CLINICAL PHARMACOLOGY

General

ERBITUX binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha. Binding of ERBITUX to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression 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 ERBITUX inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of ERBITUX were observed in human tumor xenografts lacking EGFR expression. The addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

Human Pharmacokinetics

ERBITUX administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m^2. ERBITUX clearance (CL) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution (Vd) for ERBITUX appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following a 2-hour infusion of 400 mg/m^2 of ERBITUX, the maximum mean serum concentration (Cmax) was 184 μg/mL (range: 92-327 μg/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean Cmax of 140 μg/mL (range 120-170 μg/mL). Following the recommended dose regimen (400 mg/m^2 initial dose/250 mg/m^2 weekly dose), ERBITUX concentrations

reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates including race, gender, age, and hepatic and renal function on ERBITUX pharmacokinetics.

Female patients had a 25% lower intrinsic ERBITUX clearance than male patients. The toxicity profile was similar in males and females. Definitive conclusions regarding comparability in efficacy cannot be made given the small number of patients with objective tumor responses. None of the other covariates explored appeared to have an impact on ERBITUX pharmacokinetics.

ERBITUX has not been studied in pediatric populations.

CLINICAL STUDIES

The efficacy and safety of ERBITUX alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). ERBITUX was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single-agent ERBITUX was also evaluated. All trials studied patients with EGFR-expressing, metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

Randomized, Controlled Trial

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly times four doses every 6 weeks. An Independent Radiographic Review

Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.

The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in all randomized patients.

Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen.

The objective response rates (ORR) in these populations are presented in Table 1.

Table 1: Objective Response Rates per Independent Review

Populations	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI[a])	
	n	ORR (%)	n	ORR (%)	%	p-value CMH[b]
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

[a]95% confidence interval for the difference in objective response rates.
[b]Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients

randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan experienced a significantly longer median time to disease progression (see Table 2).

Table 2: Time to Progression per Independent Review

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 – 0.71)	<0.001
• Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a]Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

Single-Arm Trials

ERBITUX, in combination with irinotecan, was studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan-containing regimen. Patients received a 20-mg test dose of ERBITUX on day 1, followed by a 400-mg/m^2 initial dose, and 250 mg/m^2 weekly until disease progression or unacceptable toxicity. Patients received the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks or 125 mg/m^2 weekly times four doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by an IRC. The overall response rate was 15% for the overall population and 12% for the irinotecan-failure population. The median durations of response were 6.5 and 6.7 months, respectively.

ERBITUX was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing, metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all-treated group and 14% for the irinotecan-failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

INDICATIONS AND USAGE

ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

ERBITUX administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

The effectiveness of ERBITUX is based on objective response rates (see **CLINICAL STUDIES**). Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX.

CONTRAINDICATIONS

None.

WARNINGS

Infusion Reactions (See BOXED WARNING: Infusion Reactions, ADVERSE REACTIONS: Infusion Reactions, and DOSAGE AND ADMINISTRATION: Dose Modifications.)

Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% (20/774) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion

reaction during later infusions. A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

Severe infusion reactions require the immediate interruption of ERBITUX therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of ERBITUX and by continued use of antihistamine medications (eg, diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic 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 receiving ERBITUX in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, ERBITUX should be discontinued and the patient should be treated appropriately.

Dermatologic Toxicity (See ADVERSE REACTIONS: Dermatologic Toxicity and DOSAGE AND ADMINISTRATION: Dose Modifications.)

In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal

passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Patients developing dermatologic toxicities while receiving ERBITUX should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future ERBITUX infusions should be instituted in case of severe acneform rash (see **DOSAGE AND ADMINISTRATION**, Table 4). Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

PRECAUTIONS

General

ERBITUX therapy should be used with caution in patients with known hypersensitivity to Cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving ERBITUX as sunlight can exacerbate any skin reactions that may occur.

EGF Receptor Testing

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation

test kit package insert for full instructions on assay performance. (See **CLINICAL STUDIES: EGFR Expression and Response.**)

Laboratory Tests: Electrolyte Monitoring

Patients should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia and hypokalemia, during and following the completion of ERBITUX therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; i.e., 8 weeks. (See **ADVERSE REACTIONS: Electrolyte Depletion.**)

Drug Interactions

A drug interaction study was performed in which ERBITUX was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between ERBITUX and irinotecan.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to ERBITUX were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving ERBITUX has not been adequately determined. The incidence of antibodies to ERBITUX was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-ERBITUX antibodies were detected in 5% (28 of 530) of evaluable patients. In patients positive for anti-ERBITUX antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to ERBITUX and the safety or antitumor activity of the molecule.

The observed incidence of anti-ERBITUX antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-ERBITUX antibody response include sample handling, timing of sample collection, concomitant medications, and

underlying disease. For these reasons, comparison of the incidence of antibodies to ERBITUX with the incidence of antibodies to other products may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test ERBITUX for carcinogenic potential. No mutagenic or clastogenic potential of ERBITUX was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of ERBITUX (based on total body surface area) revealed a tendency for impairment of menstrual cycling in treated female monkeys, including increased incidences of irregularity or absence of cycles, when compared to control animals, and beginning from week 25 of treatment and continuing through the 6-week recovery period. Serum testosterone levels and analysis of sperm counts, viability, and motility were not remarkably different between ERBITUX-treated and control male monkeys. It is not known if ERBITUX can impair fertility in humans.

Pregnancy Category C

Animal reproduction studies have not been conducted with ERBITUX. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore ERBITUX has the potential to be transmitted from the mother to the developing fetus. It is not known whether ERBITUX can cause fetal harm when administered to a pregnant woman or whether ERBITUX can affect reproductive capacity. There are no adequate and well-controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of ERBITUX treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

Nursing Mothers

It is not known whether ERBITUX is secreted in human milk. Because human IgG is secreted in human milk, the potential for absorption and harm to the infant after ingestion

exists. Based on the mean half-life of ERBITUX after multiple dosing of 114 hours [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human Pharmacokinetics**), women should be advised to discontinue nursing during treatment with ERBITUX and for 60 days following the last dose of ERBITUX.

Pediatric Use

The safety and effectiveness of ERBITUX in pediatric patients have not been established.

Geriatric Use

Of the 774 patients who received ERBITUX with irinotecan or ERBITUX monotherapy in four advanced colorectal cancer studies, 253 patients (33%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

ADVERSE REACTIONS

Except where indicated, the data described below reflect exposure to ERBITUX in 774 patients with advanced metastatic colorectal cancer. ERBITUX was studied in combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving ERBITUX plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for over 6 months], and patients receiving ERBITUX monotherapy received a median of 7 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving ERBITUX monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with ERBITUX were:

- Infusion reaction (3%) (see **BOXED WARNING, WARNINGS,** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Dermatologic toxicity (1%) (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Interstitial lung disease (0.4%) (see **WARNINGS**);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);

- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients receiving ERBITUX monotherapy;
- Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0.2% in patients receiving ERBITUX monotherapy.

Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 17 (4%) patients receiving ERBITUX monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving ERBITUX plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 420 patients receiving ERBITUX monotherapy were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%), constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in Table 3 are based on the experience of 354 patients treated with ERBITUX plus irinotecan and 420 patients treated with ERBITUX monotherapy.

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	48	10
Abdominal Pain	45	8	26	9
Fever[3]	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction[4]	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea[3]	23	2	17	7
Cough Increased	20	0	11	1

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Skin/Appendages				
Acneform Rash[5]	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

[2] Asthenia/malaise is defined as any event described as "asthenia", "malaise", or "somnolence".

[3] Includes cases reported as infusion reaction.

[4] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or "dyspnea".

[5] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

Infusion Reactions (see BOXED WARNING: Infusion Reactions)

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving ERBITUX plus irinotecan and 19% of patients receiving ERBITUX monotherapy. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

In the clinical studies described above, a 20-mg test dose was administered intravenously over 10 minutes prior to the loading dose to all patients. The test dose did not reliably identify patients at risk for severe allergic reactions.

Dermatologic Toxicity and Related Disorders

Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving ERBITUX plus irinotecan or ERBITUX monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving ERBITUX plus irinotecan and in 90% (8% Grade 3) of patients receiving ERBITUX monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

A related nail disorder, occurring in 14% of patients (0.4% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Use with Radiation Therapy

In a study of 21 patients with locally advanced squamous cell cancer of the head and neck, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port. The addition of radiation to ERBITUX therapy in patients with colorectal cancer should be done with appropriate caution.

Electrolyte Depletion

In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in

patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving ERBITUX experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS: Laboratory Tests.**)

OVERDOSAGE

Single doses of ERBITUX higher than 500 mg/m^2 have not been tested. There is no experience with overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy, is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 mL/min). Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion Reactions.**)

Dose Modifications

Infusion Reactions

If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%.

ERBITUX should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions. (See **WARNINGS** and **ADVERSE REACTIONS.)**

Dermatologic Toxicity and Related Disorders

If a patient experiences severe acneform rash, ERBITUX treatment adjustments should be made according to Table 4. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Table 4: ERBITUX Dose Modification Guidelines

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No Improvement	Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No Improvement	Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

Preparation for Administration

DO NOT ADMINISTER ERBITUX AS AN IV PUSH OR BOLUS.

ERBITUX must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

ERBITUX is supplied as a 50-mL, single-use vial containing 100 mg of Cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

USING APPROPRIATE ASEPTIC TECHNIQUE, ERBITUX SHOULD BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).

- Fill ERBITUX into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put into the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with ERBITUX before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with ERBITUX.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

ERBITUX should be piggybacked to the patient's infusion line.

Following the ERBITUX infusion, a 1-hour observation period is recommended. Longer observation periods may be required in those who experience infusion reactions.

HOW SUPPLIED

ERBITUX® (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one ERBITUX vial (NDC 66733-948-23).

Stability and Storage

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of ERBITUX in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

US Patent No. 6,217,866

ERBITUX® is a registered trademark of ImClone Systems Incorporated.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

Revised August 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084/S-030

MEDICAL REVIEW(S)

Erbitux® - STN 125084.30

LABELING SUPPLEMENT REVIEW

SUBMISSION DATE	**April 11, 2005**
ACTION DATE	**October 11, 2005**
SPONSOR	**ImClone Systems, Inc.**
PROPOSED LABELING CHANGE	**Addition of language to WARNINGS and DOSAGE AND ADMINISTRATION infusion reactions, and PRECAUTIONS and ADVERSE REACTIONS, hypomagnesemia and monitoring.**
CLINICAL REVIWER	**Lee H. Pai-Scherf, MD** LH.P-S 8/8/05 **Medical Officer, DBOP/OODP/CDER**
THROUGH:	**Joseph Gootenberg, MD, Team Leader** **Patricia Keegan, MD, Director, DBOP/OODP/CDER**
RPM	**Sharon Sickafuse**

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EXECUTIVE SUMMARY

This review is in response to a BLA supplement submitted by ImClone Systems to revise the Erbitux label WARNINGS and DOSAGE AND ADMINISTRATION infusion reactions, and PRECAUTIONS and ADVERSE REACTIONS, hypomagnesemia and monitoring.

Hypomagnesemia was not identified as a significant issue at the time of approval (Cetuximab for use in combination with irinotecan in patients with metastatic colorectal cancer having failed prior irinotecan, or as a monotherapy in patients who are irinotecan-intolerant, February 12, 2004). Subsequent to its approval, hypomagnesemia in association with other electrolyte abnormalities was observed and reported in the literature and to the FDA's Adverse Event Reporting System.

Data 244 patients from two ongoing and one completed randomized trials with Erbitux where serum magnesium was routinely monitored were reviewed. Review indicates that the incidence of hypomagnesemia (both overall and severe) was increased in patients receiving cetuximab. Hypomagnesemia was reported in 46 to 67% of the patients receiving Cetuximab, with 4 to 17% experienced severe hypomagnesemia. The overall incidence of associated hypocalcemia and hypokalemia was also increased. The onset of electrolyte abnormalities was reported to occur from 12-224 days after initiation of cetuximab. Oral and intravenous repletion was required in some patients. Based on the information available, the time to resolution of hypomagnesemia is not known. The mechanism of action by which cetuximab causes these electrolyte abnormalities is not yet known. The current package insert and a Dear Health Care Practioner letter have been revised to include this information.

In addition, based on two spontaneous post-marketing reports of late infusion reactions, the package insert has been revised to recommend adding language to extend the observation period for patients who experience any infusion reaction to Erbitux.

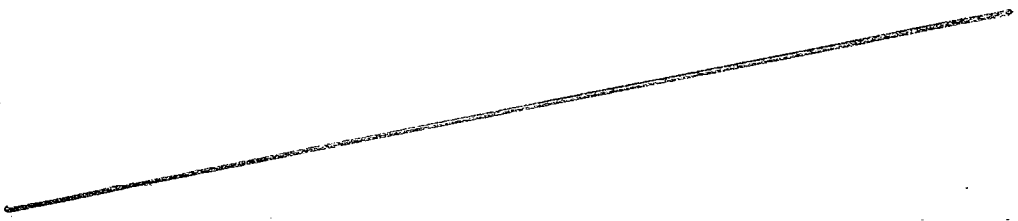
The review team recommends approval of the revised Erbitux Package Insert and Dear Health Care Practioner letter submitted by ImClone Systems on August 3, 2005.

I. BACKGROUND

On March, 2005, it came to the FDA's attention of reports of hypomagnesemia associated with cetuximab treatment. A teleconference was held on March 8, 2005 and ImClone Systems was asked to submit the relevant data and a proposed list of action items. This information was submitted to IND 5804 on March 18, 2005 (amendment 626). After review of the submission to the IND, the FDA requested a complete supplemental submission with additional information

regarding hypomagnesemia, proposed labeling changes and revisions to the Dear Health Care Practioner (DHCP) letter.

II. SPONSORS PROPOSED CHANGES (April 11, 2005 submission):



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III. FDA REVIEW OF THE DATA

The original submission of April 11, 2005 was deemed insufficient. On April 27, 2005, ImClone was asked to submit to the supplemental BLA data pertinent to hypomagnesemia from randomized trials (BMS-CA225014, ECOG E5397 and NCI CO.17) previously submitted to the IND. ImClone was also asked to provide patient narratives from all patients in the safety database who experienced hypomagnesemia including the severity of the event, the duration, when it occurred in relationship to time of Cetuximab administration, the treatment received, and the outcome. In addition, ImClone was asked to revise the package insert to include the available clinical information regarding hypomagnesemia, including severity, duration, and time to development of hypomagnesemia in relationship to cetuximab administration. ImClone was to revise the DHCP (Dear Health Care Professional) letter to include the same information.

During the same teleconference, ImClone was asked to propose changes to the package insert concerning the potential need for longer observation periods in patients experiencing severe infusion reactions. This request was prompted by two spontaneous post-marketing reports of late infusion reactions (Appendix 1).

Following is a review of the data submitted to the supplemental BLA on May 25, 2005.

A. Hypomagnesemia Database

Hypomagnesemia was not identified as a significant issue at the time of approval (Cetuximab for use in combination with irinotecan in patients with metastatic colorectal cancer having failed prior irinotecan, or as a monotherapy in patients who are irinotecan-intolerant, February 12, 2004). The Integrated Safety Summary Table (Jan 2004) included data on 1073

patients from 10 clinical trials. Overall, hypomagnesemia Grade 1-4 was reported in 53 (4.9%) patients and hypomagnesemia Grade 3-4 was reported in 13 (1.2%) patients.

Cetuximab associated hypomagnesemia was observed and reported subsequent to approval. A review of ongoing studies by ImClone, the majority of the trials did not require routine serum monitoring of magnesium, hence, the true incidence of hypomagnesemia, the time to onset and resolution were no being captured. Within the clinical database, ImClone identified two ongoing randomized trials (BMS-CA225014, ECOG E5397), and one completed randomized trial (NCI CO.17) which required serum magnesium levels to be obtained at baseline and at every subsequent cycle. Available data from these 3 trials are submitted for review. In addition, a cumulative search of the Bristol-Myers Squibb Corporate Adverse Events Reporting and Evaluation System (CARES) was conducted. Information on 13 post marketing reports of hypomagnesemia in association with cetuximab therapy were identified and included in this submission.

1. Clinical Trial Database

a) **BMS-CA225014** "A Phase III Randomized Multicenter Study of Cetuximab, Oxaliplatin, 5- Fluouracil and Leucovorin in Patients with Previously Treated Metastatic, EGFr-Positive Colorectal Carcinoma". This is an ongoing trial that includes patients with metastatic EGFr positive colorectal cancer who have received irinotecan-based chemotherapy in colorectal cancer who have received irinotecan-based chemotherapy in the 1st line setting who are randomized to receive either Erbitux in combination with FOLFOX, or FOLFOX 4 alone. Cycles of therapy are administered every 2 weeks, and serum magnesium monitoring is required at baseline and at each cycle. Hypomagnesemia data is available for 88 patients (48 in cetuximab plus FOLFOX arm and 40 in FOLFOX alone arm).

b) **ECOG 5397** "A Randomized Double Blind, Placebo Controlled Phase III Evaluation of Cisplatin plus Placebo versus Cisplatin plus C225, a Mouse/Human Monoclonal Antibody to the Epidermal Growth Factor Receptor, in Patients with Metastatic and/or Recurrent Squamous Cell Cancer of the Head and Neck" was conducted by the Eastern Cooperative Oncology Group (ECOG) between June-1999 and June, 2001. The study included patients with squamous cell cancer of the head and neck who had not received prior chemotherapy. Patients were randomized to receive either cetuximab in combination with cisplatin, or placebo in combination with cisplatin. Cycles of therapy were administered every 4 weeks, and serum magnesium monitoring

was required at baseline and at every cycle. Hypomagnesemia data is available for 112 patients (58 in Cetuximab plus cisplatin arm and 58 in cisplatin alone arm).

c) **NCIC CO.17 (BMS CA225025)** "A Phase III Randomized Study of Cetuximab (Erbitux™, C225) and Best Supportive Care versus Best Supportive Care in Patients with Pretreated Metastatic Epidermal Growth Factor Receptor (EGFr)-Positive Colorectal Carcinoma" is currently being conducted at sites in Canada, Australia, New Zealand, and Singapore. The study includes patients with EGFr-positive metastatic colorectal cancer who have received prior Fluouracil, irinotecan, and Oxaliplatin. Cycles are repeated every 4 weeks, and serum magnesium is required at baseline and at every cycle in both treatment arms. Hypomagnesemia data is available for 135 patients (138 in Cetuximab plus BSC arm and 97 in BSC alone arm).

Incidence and Severity of Hypomagnesemia

The overall incidence of hypomagnesemia and the incidence of grade 3-4 hypomagnesemia available from the randomized trials as summarized in Table I.

Table I

Incidence of Hypomagnesemia for BMS CA225014, ECOG 5397 and NCIC CO.17

	BMS CA225014		ECOG 5397		NCIC CO.17	
Hypomagnesemia	Cetuximab plus FOLFOX	FOLFOX	Cetuximab plus cisplatin	Cisplatin	Cetuximab plus BSC	BSC
All Grades (%)	22/48 (46)	8/40 (20)	39/58 (67)	26/58 (45)	66/138 (48)	14/97 (14)
Grades 3-4 (%)	8/48 (17)	0/40 (0)	8/58 (14)	0/58 (0)	5/138 (4)	0/97

The overall incidence of hypomagnesemia was higher in the cetuximab containing arm than control arm in all three randomized studies (46 % vs. 20 % in BMS CA225014 trial, 67 vs. 45% in ECOG 5397 and 48 vs. 14 % in NCIC CO.16). Furthermore, the incidence of grade 3-4 hypomagnesemia was 17 % (BMS CA225014), 14 % (ECOG 5397) and 4 % (NCIC CO.16) in cetuximab containing arms and 0 (zero) % in the control arms in all three studies.

Time of onset and clinical manifestations of hypomagnesemia

Time to onset of hypomagnesemia is available for study BMS CA225014 for patients who were not hypomagnesemic at baseline. The median time from start of treatment to onset of any grade hypomagnesemia was 56 days (range 12-224) and the median time to onset to grade 3-4 hypomagnesemia was 102.5 days (range 43-205). In the FOLFOX 4 alone treatment arm, the median time from start of treatment to onset of any grade hypomagnesemia was 63 days (range 36-226). Since the study is ongoing, the data is in the process of being confirmed and thus is considered preliminary.

Grade 1-2 sensory neuropathy was reported in 9/21 patients with grade 3-4 hypomagnesemia. One patient with baseline grade 1 sensory neuropathy progressed to grade 3 sensory and grade 3 motor neuropathy. Grade 2-3 fatigue was reported in 13 patients. No eletrocardiographic changes were reported, although hone patient experienced "palpitation".

Magnesium repletion and outcome

Information derived from case narratives from 21 patients who experienced Grade 3-4 hypomagnesemia showed that 5 (25%) received oral magnesium, 2 patients (10%) received intravenous magnesium replacement, 7 (33 %) received both oral and intravenous magnesium replacement. Management of hypomagnesemia was unknown in 7 patients (33%).

The outcome of hypomagnesemia could not be fully evaluated given the paucity of the available data. Hypomagnesemia resolved to grade 0 in 4 patients (22%) on date of discharge from study (34-42 days), three patients had grade 1 hypomagnesemia at the time of study discharge, one patient had grade 2 at the time of study discharge, one patients had grade 3 hypomagnesemia continued 7 days after last cetuximab dose, one patient had continued grade 4 hypomagnesemia despite aggressive attempts at repletion, one patient had hypermagnesemia as a result of aggressive repletion. Outcome of grade 3-4 hypomagnesemia was unknown in 8 out of 21 patients.

Associated hypocalcemia and hypokalemia

The incidence of associated hypocalcemia and serum potassium were analyzed. The overall incidence of hypocalcemia and hypokalemia were higher in the cetuximab containing arm, but minimal to no difference was noted in the incidence of grade 3-4 hypocalcemia and hypokalemia (Table II, from sponsor's submission, page 13).

Table II
Hypomagnesemia Associated Incidence of Hypocalcemia and Hypokalemia

		↓ MG^{++}		↓ CA^{++}		↓ K^{+}	
		All Grades (%)	Grades 3-4 (%)	All grades	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
BMS CA225014	Cetuximab Plus FOLFOX	22/48 (46)	8/48 (17)	28/47 (60)	7/47 (15)	32/49 (65)	5/50 (10)
	FOLFOX	8/40 (20)	0/40 (0)	16/46 (35)	3/47 (6)	19/49 (39)	5/50 (10)
EGOC 5397	Cetuximab plus cisplatin	39/58 (67)	8/58 (14)	29/58 (50)	0/58 (0)	21/58 (36)	6/58 (10)
	Cisplatin	26/58 (45)	0/58 (0)	16/58 (28)	3/58 (5)	18/58 (31)	6/58 (10)
NCIC CO.17	Cetuximab plus BSC	66/138 (5=48)	5/138 (4)	61/148 (41)	3/148 (2)	34/158 (22)	5/158 (3)
	BSC	14/97 (14)	0/97 (0)	40/112 (36)	1/112 (1)	18/128 (14	4/128 (3)

2. Post marketing Reports in the Pharmacovigilance Database

As of April 30, 2005, thirteen post marketing reports of hypomagnesemia in association with cetuximab therapy have been received by the Sponsor from worldwide sources. Hypomagnesemia was considered to have been serious in 11/13 cases. Eight/13 cases related the duration of cetuximab treatment at the time that hypomagnesemia were discovered. The time of onset of hypomagnesemia could not be accurately determined because blood magnesium levels were likely not assayed on regular intervals and the baseline values are not known. Four/13 patients had associated symptoms: asthenia, leg cramps and neuropathy. One patient with asthenia and grade 3 neuropathy of the lower extremities recovered after repletion of magnesium. 7/13 patients received intravenous replacement with or without oral supplementation.
Given the limited data contained in the spontaneous case reports preclude any detailed analysis or conclusions regarding cetuximab associated hypomagnesemia.

B. Post-marketing Reports of Late Infusion Reactions
Two spontaneous post-marketing reports of late "anaphylatoid" reactions were received from Bristol Myers Squibb via FDA's Adverse Event Reporting System (AERS) since drug approval (Appendix 1):

1. A physician reported that a male patient with metastatic colorectal cancer received the 1st infusion of cetuximab on [redacted] in an outpatient center. Approximately 10 minutes into the infusion, the patient

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experienced pruritus and facial flushing, a "lump in his throat". The infusion was discontinued, the patient was given a glass or water and the event apparently resolved after 15 minutes. One hour later, symptoms recurred with difficulty in swallowing. P_{02} was reported to be 82%. The patient became less responsive, underwent cardio respiratory arrest. Cardiopulmonary resuscitation was unsuccessful. The case was reported as "death due to acute anaphylactic reaction following cetuximab infusion".

2. An oncology nurse reported that a male patient with colorectal cancer admitted for the initial cetuximab infusion complained of pain and underwent cardio respiratory arrest. The patient responded to treatment, and was extubated. Within a short time frame, the patient arrested again and did not respond to a second resuscitation attempt.

Reviewer's comments and conclusions

Hypomagnesemia

Review of the controlled clinical trials BMS CA225014, ECOG 5397 and NCIC CO.17 indicates that the incidence of hypomagnesemia (both overall and severe) was increased in patients receiving cetuximab. The NCIC CO.17 study is considered particularly informative since cetuximab is administered as monotherapy. Hypomagnesemia was reported in 46 to 67% of the patients receiving Cetuximab, with 4 to 17% experienced severe hypomagnesemia. The overall incidence of associated hypocalcemia and hypokalemia was also increased. The onset of electrolyte abnormalities was reported to occur from 12-224 days after initiation of cetuximab. Oral and intravenous repletion was required in some patients. Based on the information available, the time to resolution of hypomagnesemia is not known. The mechanism of action by which cetuximab causes these electrolyte abnormalities is not yet known.

Late infusion reactions

Despite the limited medical information that characterizes spontaneous post marketing adverse event reports, these two cases underscore the importance of continuing monitoring of patients who experience Erbitux related infusion reactions. The present Package Insert recommends a 1-hour observation period following the Erbitux infusion. We recommend adding language to extend the observation period for patients who experience any infusion reaction to Erbitux.

IV. ACTIONS

A. FDA PROPOSED LANGUAGE FOR PACKAGE INSERT

Based on the above review, the FDA proposed the following revisions and additions to the package insert (italic):
Laboratory Tests: Electrolyte Monitoring

Patients should be periodically monitored for hypomagnesemia, hypocalcemia, and hypokalemia during and following the completion of ERBITUX therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; e.g., 6 months or more. (See **ADVERSE REACTIONS: Electrolyte Depletion.)**

ADVERSE REACTIONS

Electrolyte *Depletion*

In controlled clinical trials, the incidence of hypomagnesemia (both overall and severe [NCI-CTC Grades 3 and 4] was increased in patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of the patients receiving ERBITUX experienced hypomagnesemia; 10-15% of patients receiving ERBITUX experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence continued monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS: Laboratory Tests**.)

WARNINGS

INFUSION REACTIONS

A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

PREPARATION FOR ADMINISTRATION

Following the ERBITUX infusion, a 1-hour observation period is recommended. *Longer observation periods may be required in those who experience infusion reactions.*

B. DEAR HEALTH CARE PROVIDER LETTER

The FDA recommended the following revisions (italic) to the HCP letter:

Re: Important *Drug Warning*

Dear Healthcare Provider:

ImClone Systems Incorporated and Bristol-Myers Squibb Company are fully committed to assuring timely dissemination of safety information about their products to the healthcare community. We are writing to inform you of changes to the ***WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION*** sections of the ERBITUX® (Cetuximab) prescribing information.

*The **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections have been revised to include language regarding the recommended length of observation following ERBITUX infusion.*

*In addition, the **PRECAUTIONS** and **ADVERSE REACTIONS** sections have been revised to include language that an increased incidence of hypomagnesemia, hypocalcemia, and hypokalemia in patients receiving ERBITUX has been demonstrated*

in several randomized, controlled clinical trials. Patients in these trials received ERBITUX either with chemotherapy or as a single agent. The mechanism of this electrolyte depletion is unknown.

The following changes and additions have been made to the U.S. Package Insert for ERBITUX:

1. The following sentences were added to the Infusion Reactions subsection of the **WARNINGS** section:

   A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

2. The following sentence was added to the Preparation for Administration subsection of the **DOSAGE AND ADMINISTRATION** section:

   Longer observation periods may be required in those who experience infusion reactions.

3. A new Laboratory Tests; Electrolyte Monitoring subsection has been added to the **PRECAUTIONS** section and contains the following language:

   LABORATORY TESTS: ELECTROLYTE MONITORING
   Patients should be periodically monitored for hypomagnesemia, hypocalcemia, and hypokalemia during and following the completion of ERBITUX therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; e.g., 6 months or more. (See **ADVERSE REACTIONS: Electrolyte Depletion**.)

4. A new Electrolyte *Depletion* subsection has been added under the **ADVERSE REACTIONS** section and contains the following language:

   ELECTROLYTE *DEPLETION*
   In controlled clinical trials, the incidence of hypomagnesemia (both overall and severe [NCI-CTC Grades 3 and 4] was increased in patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of the patients receiving ERBITUX experienced hypomagnesemia; 10-15% of patients receiving ERBITUX experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence continued monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS: Laboratory Tests**.)

V. SPONSORS RESPONSE

In addition to minor editorial changes, ImClone Systems proposed the following (italic):

A. On Laboratory Tests: Electrolyte Monitoring section: Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; *i.e,. 8 weeks*. This proposal was accepted by the FDA, taken into consideration that the half-life of Erbitux is 120 -200 hours.
B. On Electrolyte Depletion section, ImClone added: "*In 244 patients evaluated* in ongoing, controlled clinical trials, the incidence of

hypomagnesemia..." This change is accurate and was accepted by the FDA.

VI. RECOMMENDATION

The revised package insert (Appendix 2) and DHCP letter (Appendix 3) was submitted to the FDA on August 3, 2005.

The review team recommends approval of the revised package insert and DHCP letter.

Appendix 1

Spontaneous post-marketing reports of late infusion reactions from Adverse Event Reporting System (AERS)

Adverse Event Reporting System (AERS)

Standard Report

Line Listing of ISRs with Narrative

Run by: ROBERT PRATT Date - Time: 04/27/2005 - 01:04 pm

Search Criteria:

Manufacturer Type: Sender of ISR

Search Type: ISR
Search for reactions listed: ANY
FDA Rcvd. Date: From:
Reporter Domestic:
Reporter First Name:
Null Values for Country:
Female:
Age Range: From:
MedWatch Source Study:
MedWatch Source Health Professional:
Expedited (15-Day) ISR:
RA Summary ISR:
Include Deactived ISRs:
Non-Serious Outcome:
Event End Date:
OTC Products Only:

Include Concomitant Products:
ISR/Case #: 4530099-
FDA Rcvd. Date: To:
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature:
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products:
Mfr. Control #:
Sort in Descending Order:
Reporter Last Name:
Reporter State:
Male:
Null Gender Values:
Age Range: YEAR
MedWatch Source Consumer:
Periodic ISR:
5 Day ISR:
Follow-up:
Serious Outcome:
Event Start Date:
ReC:

Non-Excluded Product(s) for Selected Active Ingredient(s):

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
Line Listing of ISRs with Narrative

FDA Rcvd. Date	Case	ISR/Best Rep. Ind.	Mfr. Control #	ISR Type	Age	Gender	Country	State	Outcome
12/17/2004	4182708	4530099-3 *	US-BRISTOL-MYERS SQUIBB COMPANY-12655734	Expedited (15-Day)	YR	Male			DE

Product	S/C	Indication	Daily Dose/Unit	Route	Duration/Unit	DeC	ReC	Lot	Dosage Text
Erbitux	S	COLORECTAL CANCER METASTATIC		INTRAVENOUS					Loading dose
Benadryl	C	PREMEDICATION		INTRAVENOUS	1 Days				

MedDRA Reaction

ANAPHYLACTIC REACTION

Narrative

A physician reported to a BMS sales representative that a male patient expired sometime after he received a loading dose of cetuximab. The loading dose of cetuximab (indication, dosing and therapy date not provided) was administered at an outpatient infusion center "sometime last week", and the patient expired sometime after receiving the cetuximab. The date and cause of death were not reported. The physician who reported this event to the BMS sales representative was not the patient's physician. Supplemental information received on 10-Aug-2004 from the patient's attending physician reported that the patient expired due to "anaphylactic complications" after receiving the first dose of cetuximab. The first infusion of intravenous (IV) cetuximab was administered on 29-Jul-2004 for the indication of metastatic colorectal cancer, and cetuximab was infused at a rate recommended per the United States Pharmacopoeia insert (USPI) (specific dosing and rate not reported). Approximately 10 minutes into the infusion, the patient started to complain of pruritis and facial flushing. Shortly thereafter, he stated that he had a "lump in his throat". His blood pressure at this time was 190/100. The infusion was then discontinued and fifteen minutes later, the event apparently resolved; the patient received a glass of water and noted the symptoms as greatly improved. One hour later, however, the patient went into the men's room and upon returning, reported the same signs as previously indicated. Additionally, a significant difficulty in swallowing was reported. Partial pressure of oxygen (PO2) at this time was 82 % and the patient's blood pressure was 150/86. Emergency medical services (EMS) were then called. During transit time, the patient became less responsive and upon arrival of EMS, intubation was attempted but failed. Cardiopulmonary resuscitation (CPR) was subsequently administered in conjunction with unspecified cardiotonic agents. The patient was transported to the emergency room (ER) at a nearby hospital where he was found to be without respirations. Consequently, a transcutaneous pacemaker was inserted and an emergent tracheostomy was performed. Unfortunately, all of these actions were of no avail and the patient expired, per the reporter, due to anaphylactic complications. The patient had been experiencing dyspnea for a duration of one week prior to the administration of cetuximab. He had no allergies and was negative for medical history aside from Stage 4 colorectal cancer with disease progression to the pelvis and lungs bilaterally. Supplemental information was received on 19-Oct-2004 from the Food and Drug Administration (FDA): A physician (forensic pathologist) from a Medical Examiners Office reported to the FDA Central Triage Unit (sequence number 228403E) that a male patient expired due to an acute anaphylactic reaction following a cetuximab infusion. Therapy with intravenous (IV) cetuximab was administered for the first time on [redacted] for the indication of metastatic colon cancer. Autopsy and microscopic examination were performed (results not provided). Additional information was received on 21-Oct-2004 from a nurse at the office of the initial reporting phvsician. The nurse confirmed that the male patient had a weight of 295 pounds and that cetuximab had been administered on [redacted] not 29-Jul-2004 as had initially been reported. The date of death was confirmed as [redacted]. Supplemental information received on 10-Dec-2004 by an ImClone sales representative from a pharmacist at the clinic reported that the patient had received diphenhydramine IV as a premedication and that the patient had received about 1/4 of the cetuximab infusion when he went into anaphylactic shock. The paramedics responded within 9 minutes, but the patient had expired before they arrived.

b(6)

FDA - Adverse Event Reporting System (AERS)
Standard Report
Line Listing of ISRs with Narrative

FDA Rcvd. Date	Case	ISR/Best Rep. Ind.	Mfr. Control #	ISR Type	Age	Gender	Country	State	Outcome
Product	S/C	Indication	Daily Dose/Unit	Route	Duration/Unit	DeC	ReC	Lot	Dosage Text
MedDRA Reaction									
Narrative									
11/30/2004	5685153	4513407-9 *	US-BRISTOL-MYERS SQUIBB COMPANY-12704862	Periodic	YR	Male			DE
Erbitux	S			INTRAVENOUS					Initial infusion
ANAPHYLACTIC SHOCK		PAIN							

An oncology registered nurse reported to a BMS oncology representative that a male patient (age not provided) developed anaphylactic shock and died after receiving intravenous cetuximab. The patient was hospitalized for an undisclosed diagnosis and he received a cetuximab treatment. The reporter was not sure if this was the patient's initial treatment with cetuximab (dosing not reported). Reportedly, per the instruction of patient's oncologist, no any premedication was given prior to the cetuximab administration. During the infusion, the patient developed anaphylactic shock. The treatment was stopped, and the patient remained in the hospital where he passed away a day or so later. Supplemental information received on 11-Oct-2004 by a BMS Oncology Medical Liaison from an oncology nurse attending an "Erbitux CORE presentation" reported that the patient had been placed in the hospital for the initial cetuximab infusion by one of the local medical oncologists. The patient was a "colorectal patient". No pre-medications were administered prior to the cetuximab infusion. The nurse relates that the infusion was started and the patient complained of pain. She left the room to obtain pain medication. She was out of the room retrieving pain medication when the patient's daughter ran into the hall calling for help. Emergency medical management and cardiopulmonary resuscitation (CPR) were administered along with endotracheal intubation. The patient responded to treatment, was awake, began talking and was extubated. Within a short time frame the patient arrested again and did not respond to a second resuscitation attempt. The nurse reported that the pathologist stated that there was significant pulmonary disease and lysis noted.

Adverse Event Reporting System (AERS)

Standard Report

Line Listing of ISRs with Narrative

Run by: ROBERT PRATT Date - Time: 04/27/2005 - 01:07 pm

Search Criteria:

Manufacturer Type: Sender of ISR

Search Type: ISR
Search for reactions listed: ANY
FDA Rcvd. Date: From:
Reporter Domestic:
Reporter First Name:
Null Values for Country:
Female:
Age Range: From:
MedWatch Source Study:
MedWatch Source Health Professional:
Expedited (15-Day) ISR:
RA Summary ISR:
Include Deactived ISRs:
Non-Serious Outcome:
Event End Date:
OTC Products Only:

Include Concomitant Products:
ISR/Case #: 4513407-
FDA Rcvd. Date: To:
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature:
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products:
Mfr. Control #:
Sort in Descending Order:
Reporter Last Name:
Reporter State:
Male:
Null Gender Values:
Age Range: YEAR
MedWatch Source Consumer:
Periodic ISR:
5 Day ISR:
Follow-up:
Serious Outcome:
Event Start Date:
ReC:

Non-Excluded Product(s) for Selected Active Ingredient(s):

Excluded Product(s) for Selected Active Ingredient(s):

Appendix 2

Revised Package Insert

Rx only

ERBITUX®

(Cetuximab)

For intravenous use only.

WARNING

Infusion Reactions: Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension (see **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions require immediate interruption of the ERBITUX infusion and permanent discontinuation from further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

DESCRIPTION

ERBITUX® (Cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). ERBITUX is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. ERBITUX is produced in mammalian (murine myeloma) cell culture.

ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

CLINICAL PHARMACOLOGY

General

ERBITUX binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor–alpha. Binding of ERBITUX to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression 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 ERBITUX inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of ERBITUX were observed in human tumor xenografts lacking EGFR expression. The addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

Human Pharmacokinetics

ERBITUX administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m^2. ERBITUX clearance (CL) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution (Vd) for ERBITUX appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following a 2-hour infusion of 400 mg/m^2 of ERBITUX, the maximum mean serum concentration (Cmax) was 184 μg/mL (range: 92-327 μg/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean Cmax of 140 μg/mL (range 120-170 μg/mL). Following the recommended dose regimen (400 mg/m^2 initial dose/250 mg/m^2 weekly dose), ERBITUX concentrations

reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates including race, gender, age, and hepatic and renal function on ERBITUX pharmacokinetics.

Female patients had a 25% lower intrinsic ERBITUX clearance than male patients. The toxicity profile was similar in males and females. Definitive conclusions regarding comparability in efficacy cannot be made given the small number of patients with objective tumor responses. None of the other covariates explored appeared to have an impact on ERBITUX pharmacokinetics.

ERBITUX has not been studied in pediatric populations.

CLINICAL STUDIES

The efficacy and safety of ERBITUX alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). ERBITUX was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single-agent ERBITUX was also evaluated. All trials studied patients with EGFR-expressing, metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

Randomized, Controlled Trial

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly times four doses every 6 weeks. An Independent Radiographic Review

Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ≥80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.

The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in all randomized patients.

Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen.

The objective response rates (ORR) in these populations are presented in Table 1.

Table 1: Objective Response Rates per Independent Review

Populations	ERBITUX + Irinotecan n	ERBITUX + Irinotecan ORR (%)	ERBITUX Monotherapy n	ERBITUX Monotherapy ORR (%)	Difference (95% CI[a]) %	p-value CMH[b]
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
• Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8 - 25.6)	0.09
• Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

[a]95% confidence interval for the difference in objective response rates.
[b]Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients

randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan experienced a significantly longer median time to disease progression (see Table 2).

Table 2: Time to Progression per Independent Review

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 – 0.71)	<0.001
• Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
• Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a]Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

Single-Arm Trials

ERBITUX, in combination with irinotecan, was studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan-containing regimen. Patients received a 20-mg test dose of ERBITUX on day 1, followed by a 400-mg/m^2 initial dose, and 250 mg/m^2 weekly until disease progression or unacceptable toxicity. Patients received the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks or 125 mg/m^2 weekly times four doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by an IRC. The overall response rate was 15% for the overall population and 12% for the irinotecan-failure population. The median durations of response were 6.5 and 6.7 months, respectively.

ERBITUX was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing, metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all-treated group and 14% for the irinotecan-failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

INDICATIONS AND USAGE

ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

ERBITUX administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

The effectiveness of ERBITUX is based on objective response rates (see **CLINICAL STUDIES**). Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX.

CONTRAINDICATIONS

None.

WARNINGS

Infusion Reactions (See BOXED WARNING: Infusion Reactions, ADVERSE REACTIONS: Infusion Reactions, and DOSAGE AND ADMINISTRATION: Dose Modifications.)

Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% (20/774) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion

reaction during later infusions. A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

Severe infusion reactions require the immediate interruption of ERBITUX therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of ERBITUX and by continued use of antihistamine medications (eg, diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic 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 receiving ERBITUX in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, ERBITUX should be discontinued and the patient should be treated appropriately.

Dermatologic Toxicity (See ADVERSE REACTIONS: Dermatologic Toxicity and DOSAGE AND ADMINISTRATION: Dose Modifications.)

In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal

passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Patients developing dermatologic toxicities while receiving ERBITUX should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future ERBITUX infusions should be instituted in case of severe acneform rash (see **DOSAGE AND ADMINISTRATION**, Table 4). Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

PRECAUTIONS

General

ERBITUX therapy should be used with caution in patients with known hypersensitivity to Cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving ERBITUX as sunlight can exacerbate any skin reactions that may occur.

EGF Receptor Testing

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation

test kit package insert for full instructions on assay performance. (See **CLINICAL STUDIES: EGFR Expression and Response.**)

Laboratory Tests: Electrolyte Monitoring

Patients should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia and hypokalemia, during and following the completion of ERBITUX therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; i.e., 8 weeks. (See **ADVERSE REACTIONS: Electrolyte Depletion.**)

Drug Interactions

A drug interaction study was performed in which ERBITUX was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between ERBITUX and irinotecan.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to ERBITUX were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving ERBITUX has not been adequately determined. The incidence of antibodies to ERBITUX was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-ERBITUX antibodies were detected in 5% (28 of 530) of evaluable patients. In patients positive for anti-ERBITUX antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to ERBITUX and the safety or antitumor activity of the molecule.

The observed incidence of anti-ERBITUX antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-ERBITUX antibody response include sample handling, timing of sample collection, concomitant medications, and

underlying disease. For these reasons, comparison of the incidence of antibodies to ERBITUX with the incidence of antibodies to other products may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test ERBITUX for carcinogenic potential. No mutagenic or clastogenic potential of ERBITUX was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of ERBITUX (based on total body surface area) revealed a tendency for impairment of menstrual cycling in treated female monkeys, including increased incidences of irregularity or absence of cycles, when compared to control animals, and beginning from week 25 of treatment and continuing through the 6-week recovery period. Serum testosterone levels and analysis of sperm counts, viability, and motility were not remarkably different between ERBITUX-treated and control male monkeys. It is not known if ERBITUX can impair fertility in humans.

Pregnancy Category C

Animal reproduction studies have not been conducted with ERBITUX. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore ERBITUX has the potential to be transmitted from the mother to the developing fetus. It is not known whether ERBITUX can cause fetal harm when administered to a pregnant woman or whether ERBITUX can affect reproductive capacity. There are no adequate and well-controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of ERBITUX treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

Nursing Mothers

It is not known whether ERBITUX is secreted in human milk. Because human IgG is secreted in human milk, the potential for absorption and harm to the infant after ingestion

exists. Based on the mean half-life of ERBITUX after multiple dosing of 114 hours [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human Pharmacokinetics**), women should be advised to discontinue nursing during treatment with ERBITUX and for 60 days following the last dose of ERBITUX.

Pediatric Use

The safety and effectiveness of ERBITUX in pediatric patients have not been established.

Geriatric Use

Of the 774 patients who received ERBITUX with irinotecan or ERBITUX monotherapy in four advanced colorectal cancer studies, 253 patients (33%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

ADVERSE REACTIONS

Except where indicated, the data described below reflect exposure to ERBITUX in 774 patients with advanced metastatic colorectal cancer. ERBITUX was studied in combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving ERBITUX plus irinotecan received a median of 12 doses [with 88/354 (25%) treated for over 6 months], and patients receiving ERBITUX monotherapy received a median of 7 doses [with 36/420 (9%) treated for over 6 months]. The population had a median age of 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving ERBITUX monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with ERBITUX were:

- Infusion reaction (3%) (see **BOXED WARNING, WARNINGS,** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Dermatologic toxicity (1%) (see **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Interstitial lung disease (0.4%) (see **WARNINGS**);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);

- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients receiving ERBITUX monotherapy;
- Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0.2% in patients receiving ERBITUX monotherapy.

Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 17 (4%) patients receiving ERBITUX monotherapy discontinued treatment primarily because of adverse events.

The most common adverse events seen in 354 patients receiving ERBITUX plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 420 patients receiving ERBITUX monotherapy were acneform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%), constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in Table 3 are based on the experience of 354 patients treated with ERBITUX plus irinotecan and 420 patients treated with ERBITUX monotherapy.

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	48	10
Abdominal Pain	45	8	26	9
Fever[3]	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction[4]	19	3	21	2
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea[3]	23	2	17	7
Cough Increased	20	0	11	1

Table 3: Incidence of Adverse Events (≥10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Skin/Appendages				
Acneform Rash[5]	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

[2] Asthenia/malaise is defined as any event described as "asthenia", "malaise", or "somnolence".

[3] Includes cases reported as infusion reaction.

[4] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever", or "dyspnea".

[5] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis".

Infusion Reactions (see BOXED WARNING: Infusion Reactions)

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving ERBITUX plus irinotecan and 19% of patients receiving ERBITUX monotherapy. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

In the clinical studies described above, a 20-mg test dose was administered intravenously over 10 minutes prior to the loading dose to all patients. The test dose did not reliably identify patients at risk for severe allergic reactions.

Dermatologic Toxicity and Related Disorders

Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving ERBITUX plus irinotecan or ERBITUX monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving ERBITUX plus irinotecan and in 90% (8% Grade 3) of patients receiving ERBITUX monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

A related nail disorder, occurring in 14% of patients (0.4% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Use with Radiation Therapy

In a study of 21 patients with locally advanced squamous cell cancer of the head and neck, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port. The addition of radiation to ERBITUX therapy in patients with colorectal cancer should be done with appropriate caution.

Electrolyte Depletion

In 244 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in

patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving ERBITUX experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS: Laboratory Tests**.)

OVERDOSAGE

Single doses of ERBITUX higher than 500 mg/m^2 have not been tested. There is no experience with overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy, is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 mL/min). Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion Reactions**.)

Dose Modifications

Infusion Reactions

If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%.

ERBITUX should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions. (See **WARNINGS** and **ADVERSE REACTIONS.)**

Dermatologic Toxicity and Related Disorders

If a patient experiences severe acneform rash, ERBITUX treatment adjustments should be made according to Table 4. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Table 4: ERBITUX Dose Modification Guidelines

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No Improvement	Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No Improvement	Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

Preparation for Administration

DO NOT ADMINISTER ERBITUX AS AN IV PUSH OR BOLUS.

ERBITUX must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

ERBITUX is supplied as a 50-mL, single-use vial containing 100 mg of Cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

USING APPROPRIATE ASEPTIC TECHNIQUE, ERBITUX SHOULD BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).

- Fill ERBITUX into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put into the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with ERBITUX before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with ERBITUX.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

ERBITUX should be piggybacked to the patient's infusion line.

Following the ERBITUX infusion, a 1-hour observation period is recommended. Longer observation periods may be required in those who experience infusion reactions.

HOW SUPPLIED

ERBITUX® (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one ERBITUX vial (NDC 66733-948-23).

Stability and Storage

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of ERBITUX in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

US Patent No. 6,217,866

ERBITUX® is a registered trademark of ImClone Systems Incorporated.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

Revised August 2005

Appendix 3

Revised Dear Health Care Provider Letter

July 26, 2005

Re: Important Drug Warning

Dear Healthcare Provider:

ImClone Systems Incorporated and Bristol-Myers Squibb Company are fully committed to assuring timely dissemination of safety information about their products to the healthcare community. We are writing to inform you of changes to the **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the ERBITUX® (Cetuximab) prescribing information.

The **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections have been revised to include language regarding the recommended observation periods following an ERBITUX infusion and in patients who experience infusion reactions.

In addition, the **PRECAUTIONS** and **ADVERSE REACTIONS** sections have been revised to include language regarding an increased incidence of hypomagnesemia seen in ERBITUX clinical trials and recommendations for electrolyte monitoring.

The following changes and additions have been made to the U.S. Package Insert for ERBITUX:

1. The following sentences were added to the Infusion Reactions subsection of the **WARNINGS** section:

   A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

2. The following sentence was added to the Preparation for Administration subsection of the **DOSAGE AND ADMINISTRATION** section:

   Longer observation periods may be required in those who experience infusion reactions.

3. A new Laboratory Tests: Electrolyte Monitoring subsection has been added to the **PRECAUTIONS** section and contains the following language:

   LABORATORY TESTS: ELECTROLYTE MONITORING

   Patients should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia and hypokalemia, during and following the completion of ERBITUX therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; i.e., 8 weeks. (See **ADVERSE REACTIONS: Electrolyte Depletion.**)

4. A new Electrolyte Depletion subsection has been added under the **ADVERSE REACTIONS** section and contains the following language:

ELECTROLYTE DEPLETION

In 224 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving ERBITUX experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS: Laboratory Tests**.)

For any questions or to report serious adverse events suspected to be associated with the use of ERBITUX, call **1-888-ERBITUX (372-4889)**. By calling this number, you can speak to a representative directly or use our automated Faxback system to order document code number 2000, which is the Adverse Event Reporting Form. Alternatively this information may be reported to FDA's MedWatch Reporting System by phone at **1-800-FDA-1088**, by facsimile 1-800-FDA-0178, by mail using the Form 3500 at http://www.fda.gov/medwatch/index.html.

Please refer to the accompanying revised full prescribing information for ERBITUX, including **boxed WARNING regarding infusion reactions.**

Sincerely,

Eric K. Rowinsky, MD
Senior Vice President, Chief Medical Officer
ImClone Systems Incorporated

A. Collier Smyth, MD
Senior Vice President
Medical Affairs
Bristol-Myers Squibb Company

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084/S-030

OTHER REVIEW(S)

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125084/30 Product: Cetuximab Applicant: ImClone

Final Review Designation (circle one): (Standard) Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): (Traditional) CTD

Filing Meeting: Date 6-23-05 Committee Recommendation (circle one) (File) RTF

RPM: Sharon Sickafuse
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - X Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - X Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Pai-Scherf _____ _____
- ☐ Memo of Filing Meeting

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ protocols for clinical trials present	Y N	n/a
❑ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement:		
❑ description and results of studies performed to evaluate the change	Y N	
❑ relevant validation protocols	Y N	
❑ list of relevant SOPs	Y N	
if clinical supplement:		
❑ changes in labeling clearly highlighted	(Y) N	
❑ data to support all label changes	(Y) N	
❑ all required electronic components, including electronic datasets (e.g. SAS)	(Y) N	
if electronic submission:		
❑ required paper documents (e.g. forms and certifications) submitted	(Y) N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? no

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: _____

Recommendation (circle one): (File) RTF

RPM Signature: Sickafuse Branch Chief concurrence: Karen D. Jones

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y N	
▫ Biopharmaceutics and associated analytical methods	Y (N)	Not applicable
▫ Clinical pharmacology [includes immunogenicity]	Y (N)	Not applicable
▫ Clinical Efficacy [for each indication]	Y (N)	Not applicable
▫ Clinical Safety	Y (N)	Requested via teleconference on 4/27/05. Received 5/26/05
▫ Synopses of individual studies	Y (N)	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	Y (N)	Received on 5/26/05
Study Reports and related information [5.3]	Y N	
▫ Biopharmaceutic	Y (N)	Not applicable
▫ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y (N)	Not applicable
▫ Pharmacokinetics (PK)	Y (N)	Not applicable
▫ Pharmacodynamic (PD)	Y (N)	Not applicable
▫ Efficacy and Safety	(Y) N	
▫ Postmarketing experience	(Y) N	
▫ Case report forms	Y (N)	Not applicable
▫ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	Y (N)	Not applicable
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
▫ legible	(Y) N	
▫ English (or certified translation into English)	(Y) N	
▫ compatible file formats	(Y) N	
▫ navigable hyper-links	(Y) N	
▫ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	Y (N)	Not applicable
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	Y (N)	Not applicable
☐ conducted in compliance with requirements for informed consent	Y (N)	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	Safety information
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y (N)	Not applicable
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y (N)	Not applicable
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y (N)	Not applicable
drug interaction studies communicated as during IND review as necessary are included	Y (N)	Not applicable
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	Y (N)	Not applicable
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y (N)	Not applicable
adequate characterization of product specificity or mode of action	Y (N)	Not applicable
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y (N)	Not applicable
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	safety data

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
BMS CA225014	Y	(N)	Y	N	(NR)	Y	N	Y	N	(NR)
~~BMS C~~	Y	N	Y	N	NR	Y	N	Y	N	NR
ECOG 5397	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Pertinent safety information was submit to IND 5804 on March 18, 2005. This was not submitted to the sBLA. I'm have asked to resubmit all the pertinent safety information, including patient narratives who experienced hypo Magnesemia.

Information was received on May 26, 2005.

Is clinical site(s) inspection (BiMo) needed?

NO

Is an Advisory Committee needed?

NO

Recommendation (circle one): (File) RTF

Reviewer: Lee Pai-Scherf Type (circle one): (Clinical) Clin/Pharm Statistical
(signature/ date)
6/20/05

Concurrence:

Branch Chief: _____ Division. Director: PKeegan 6/23/05
(signature/ date) (signature/ date)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Memorandum

STN 125084/39

PID# D050034

DATE: May 12, 2005

FROM: Bob Pratt, Pharm.D.
Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M.
Director
Division of Drug Risk Evaluation, HFD-430

TO: Patricia Keegan, M.D.
Director
Division of Therapeutic Biological Oncology Products (DTBOP), HFD-107

SUBJECT: Postmarketing Safety Review
Drug: Erbitux (cetuximab) BLA# 125084
Event: One-Year Postmarketing Safety Profile

EXECUTIVE SUMMARY

This consult is in response to a request made January 13, 2005 by Dr. Lee Pai-Scherf (Medical Officer, DTBOP, HFD-107) to provide a broad overview of adverse event reports associated with cetuximab (Erbitux®) submitted to the Adverse Event Reporting System (AERS) since marketing approval in February 2004. As of January 27, 2005, the AERS database contained a total of 894 cases, primarily noting skin, gastrointestinal, and general disorders, that were associated with the active ingredient cetuximab or the trade name Erbitux.

The consult focuses on "watch list" events established by DTBOP[1] at the cetuximab internal safety conference held March 9, 2004, as well as serious and unlabeled events of interest found in AERS reporting patterns sorted by the MedDRA hierarchy of System Organ Class (SOC) and Preferred Terms. The "watch list" events and findings include the following:

- Interstitial lung disease, which was a rare but significant toxicity observed in the clinical trials. In terms of product labeling enhancement, there is no appreciable new clinical information from 11 cases.
- Dermatologic reactions with concomitant radiation therapy; one small clinical trial of 21 patients with head and neck cancer observed an increased incidence of rash, particularly within the radiation port. No cases were identified.

[1] These events were selected to increase the clinical knowledge base, or for the reason described.

- Use in pregnancy, as a matter of general interest. No cases were identified.
- Infusion reaction cluster reporting, as a potential signal of manufacturing issues. There is no obvious clustering noted by date of event or lot number, but several cases describe unlabeled events including cardiac arrest, respiratory arrest, and convulsions as manifestations of infusion reactions. There are also two cases that seem to describe recurrent prolonged reactions after the patient initially responded to treatment or interruption of the drug infusion. Consideration should be given to adding a description of these prolonged events and the need for extended observation/support of patients in the labeled warnings.

Serious and unlabeled events of interest identified by analysis of AERS reporting patterns include the following events and findings:

- Hypomagnesemia. Fifteen cases of hypomagnesemia were noted. Although most cases did not report serious clinical manifestations, nine of the 15 cases required supplemental IV or oral magnesium supplementation. Six cases reported grade 3/4 hypomagnesemia.[2] Two additional cases were identified from a search of the medical literature; these cases described neuromuscular symptoms and inappropriate urinary excretion of magnesium that required several weeks of IV magnesium repletion. Consideration should be given to routine monitoring of magnesium in patients receiving cetuximab, as well as in clinical situations potentially related to hypomagnesemia.
- Hepatic failure and venoocclusive disease. In the four cases reviewed, there was no clear evidence of direct hepatotoxicity mediated by cetuximab.
- Neutropenia, pancytopenia, and hemolytic anemia. Twenty-eight of the 31 cases reported neutropenia or pancytopenia in patients receiving concomitant chemotherapy labeled for such events; there is no evidence of cetuximab augmentation of neutropenia or pancytopenia. There is not a strong signal associating cetuximab with three cases of hemolytic anemia.
- Bleeding events. The eight cases reviewed all appear to be confounded.
- Bowel perforation. There are four cases of bowel perforations that occurred within two months of starting cetuximab. In two of the four cases, the perforation site was not specified; the other two cases appeared to involve perforations at sites other than the disease locations.[3] At this time, there is not a clear signal that associates cetuximab with this event

In summary, the main findings of this one-year postmarketing review include hypomagnesemia and unlabeled manifestations of infusion reactions. We will continue to monitor these events as well as all adverse events associated with the use of cetuximab.

BACKGROUND

Cetuximab is a recombinant human/mouse chimeric monoclonal antibody that binds epidermal growth factor receptor (EGFR) on normal and tumor cells and competitively inhibits the growth factor. The product is approved for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are refractory to or intolerant of irinotecan.

SEARCH STRATEGY AND RESULTS

AERS was searched for all adverse events associated with the active ingredient cetuximab and the trade name Erbitux on January 27, 2005. At that time, AERS contained a total of 894 cases[4], of

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[2] National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Grade 3/4 hypomagnesemia is defined as a serum magnesium level less than 0.9 mg/dL.

[3] A patient with metastatic carcinoma of the distal rectum experienced perforation of the ascending colon in the absence of progressive disease at that site. The second case involved a small bowel perforation and partial duodenectomy in a patient with metastatic colorectal cancer.

[4] Approximately 60 cases were premarketing clinical study reports submitted to the NDA of a concomitant drug. These cases were generally not reviewed.

which 608 reported serious outcomes including 84 deaths, 99 life threatening reactions, and 343 hospitalizations. The majority of the most frequently reported Preferred Terms in cases are mentioned in the current label[5] or are commonly found in the disease setting and include:

Rash (118), Dermatitis Acneiform (84), Diarrhoea (78), Dyspnoea (66), Dehydration (53), Infusion Related Reaction (51), Vomiting (50), Nausea (49), Hypotension (43), Pyrexia (41), Asthenia (39), Pruritus (39), Chills (38), Acne (33), Erythema (27), Anaphylactic Reaction (25), Neutropenia (25), Anaemia (22), Fatigue (22), Flushing (22), and Malignant Neoplasm Progression (22).

The SOCs with the highest case counts (and the most commonly reported Preferred Terms that fell under those SOCs) were as follows:

- Skin and Subcutaneous Tissue Disorders (373): rash, dermatitis acneiform, pruritus, acne
- General Disorders and Administration Site Conditions (286): infusion related reaction, pyrexia, asthenia, chills
- Gastrointestinal Disorders (204): diarrhoea, vomiting, nausea
- Investigations (160): blood pressure decreased, oxygen saturation decreased, haemoglobin decreased
- Respiratory, Thoracic and Mediastinal Disorders (158): dyspnoea, pulmonary embolism, bronchospasm, pneumonitis

The consult focuses on "watch list" events established by DTBOP[1] at the cetuximab internal safety conference held March 9, 2004, as well as serious and unlabeled events of interest found in AERS reporting patterns sorted by the MedDRA hierarchy of SOC and Preferred Terms. The "watch list" includes interstitial lung disease; dermatologic reactions with concomitant radiation therapy; infusion reactions; and cases in pregnancy, of which there were none. Serious and unlabeled events of interest identified by analysis of AERS reporting patterns include hypomagnesemia; hepatic failure and hepatic venoocclusive disease; blood disorders; gastrointestinal and other hemorrhages, and intestinal perforation. Each of these topics is discussed in turn.

"WATCH LIST" EVENTS

1. *Interstitial Lung Disease*

CURRENT LABELING

WARNINGS: Pulmonary Toxicity
Interstitial lung disease (ILD) was reported in 3 of 774 (<0.5%) patients with advanced colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic 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 receiving ERBITUX in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases. In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, ERBITUX should be discontinued and the patient should be treated appropriately.

CASE DEFINITION

Cases of interstitial lung disease (ILD) were defined in the following way:

- A clinical diagnosis of interstitial lung disease or interstitial pneumonia or diffuse parenchymal lung disease or alveolitis or similar terminology. Respiratory symptoms and radiologic evidence of bilateral diffuse parenchymal opacities are considered supporting information. There is usually improvement in symptoms and imaging after the drug is discontinued.

[5] Unlabeled events are underlined.

SEARCH AND RESULTS

The AERS database contained 27 unduplicated cases identified with the MedDRA terms Lower Respiratory Tract Inflammatory and Immunologic Conditions (HLT), Parenchymal Lung Disorders NEC (HLT), or Lung Disorder (PT) that were associated with the active ingredient cetuximab or the trade name Erbitux.

Of the 27 cases, 11 were selected for the series. Sixteen cases were excluded as not being drug-induced ILD based on the following:

- Microbial or aspiration pneumonia (9)
- Atelecatasis (2)
- Premarketing safety reports not reviewed (2)
- Dehydration with shortness of breath and tachycardia (1)
- Lung cancer with respiratory failure (1)
- Lung infiltration and respiratory insufficiency with infusion reaction (1)

Table 1. Characteristics of ILD cases (n=11)	
Age (years) [n=10]	Median 60.5 Range 54 to 85
Gender (n)	Male 9, Female 2
Report Source (n)	U.S. 9, Foreign 2
Report Type (n)	15-Day Expedited 7 Periodic 4
Indication (n)	Colorectal cancer 8 Non Small Cell Lung Cancer (NSCLC) 3
Doses of treatment	Median 7 Range 2 to 17
Outcome (n)	Death 4 Hospitalization 4 Disability 1
Dechallenge results (n)	Positive 3

- Four cases provided minimal information and were difficult to evaluate.
- Seven patients received steroid treatment for the ILD. In three of these cases, the report noted cetuximab was discontinued and the patient improved or recovered. One patient with pulmonary fibrosis related to prior oxaliplatin exposure experienced an exacerbation, and showed slight improvement with drug discontinuation and steroids. Of four other patients treated with steroids, two showed slight improvement (final outcome not reported), and one patient was diagnosed as having radiation pneumonitis.
- Three patients with NSCLC received radiation therapy as part of their treatment regimen. The CT scan of one of these patients showed radiation pneumonitis.
- One patient received concomitant oxaliplatin therapy and three patients received concomitant paclitaxel therapy. These drugs are labeled for pulmonary toxicity or the adverse event interstitial pneumonia. Eight patients received concomitant irinotecan, which is not similarly labeled but has been cited in literature reports as being associated with interstitial pneumonia.
- None of the cases provided biopsy results or findings from bronchoalveolar lavage.
- Of the four deaths, only one listed drug-induced disease as part of the differential diagnosis.

CONCLUSION

The cases of ILD do not provide appreciable new information for the purpose of labeling revisions.

2. *Dermatologic reactions with concomitant radiation therapy*

CURRENT LABELING

WARNINGS: Dermatologic Toxicity
In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment. In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe (Grade 3 or 4) in 11% (84/774) of these patients... (continued)

Adverse Reactions: Dermatologic Toxicity and Related Disorders
Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving ERBITUX plus irinotecan or ERBITUX monotherapy... (continued)

Use with Radiation Therapy
In a study of 21 patients with locally advanced squamous cell cancer of the head and neck, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port. The addition of radiation to ERBITUX therapy in patients with colorectal cancer should be done with appropriate caution.

SEARCH AND RESULTS

Cases were defined as any reaction reported as being related to concurrent or previous radiation therapy. The AERS database contained three unduplicated cases identified with the MedDRA term Radiation Injury (HLT). One case was excluded for having no mention of radiation therapy in a patient with a pustular, acneiform rash. Another case was excluded as a premarketing safety report from February 2000. The remaining case is described below:

- ISR# 4558259, 15-Day Report, Singapore, November 2004
  A 51 year-old female with colorectal cancer received cetuximab 400 mg weekly for five weeks. After a dilatation procedure for a urethral stricture, the patient developed hematuria and a Grade 3 hemorrhage and was hospitalized. Flexible cystoscopy showed radiation cystitis with no gross lesions. The patient was treated with antibiotics and intermittent catheterization and recovered. Cetuximab therapy was continued. Concomitant medications: tramadol, omeprazole, Neuroforte, celecoxib.

In addition, cases of serious skin toxicity that might describe radiation therapy in the narrative or medical history were selected based on the listing of Preferred Terms reported under the Skin and Subcutaneous Tissue Disorders SOC. Cases reporting Dermatitis Exfoliative, Localised Exfoliation, Localised Skin Reaction, Skin Desquamation, Skin Necrosis, Toxic Epidermal Necrolysis, and Toxic Skin Eruption were selected for review.

- Of the 11 cases identified, none described the use of radiation therapy.
- No case reported the use of doses higher than those recommended in the cetuximab labeling.
- Four cases resulted in hospitalization and involved desquamating rash (2); petechial excoriations (1); and a pruritic, papular facial reaction (1). Two of the four hospitalizations described additional contributing events, such as possible disseminated intravascular coagulation and severe leukopenia with anemia and bloody feces. An additional case of facial skin ulceration and sloughing did not require hospitalization. The skin reactions were generally managed by drug withdrawal or interruption with subsequent clinical improvement.

- One foreign case involved the unlabeled event of toxic epidermal necrolysis; a 65 year-old male with metastatic colorectal cancer experienced eczema, skin dryness, and necrotizing dermatitis five weeks after the start of cetuximab. The cutaneous lesions improved under treatment with steroids and antibiotics.
- The other five cases described non-serious rashes or skin peeling.

CONCLUSION

The cases of serious skin toxicity appear consistent with the current product labeling. There is no appreciable new information related to adverse reactions in patients receiving or having received radiation therapy.

3. *Infusion Reactions*

CURRENT LABELING

Boxed Warning:
Infusion Reactions: Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension (see WARNINGS and ADVERSE REACTIONS). Severe infusion reactions require immediate interruption of the ERBITUX infusion and permanent discontinuation from further treatment. (See WARNINGS: Infusion Reactions and DOSAGE AND ADMINISTRATION: Dose Modifications.)[6]

CASE DEFINITION

An infusion reaction was defined as cases that developed signs or symptoms during or shortly after drug infusion and reported at least one of the following search terms: Anaphylactic Responses (HLT), Bronchospasm (PT), Cold Sweat (PT), Cyanosis (PT), Flushing (PT), Hypersensitivity (PT), Hypotension (PT), Infusion Related Reaction (PT), Respiratory Arrest (PT), Swelling Face (PT), Wheezing (PT).

SEARCH AND RESULTS

AERS contained 166 unduplicated cases identified by the search terms above. Of the 166 cases, 26 were excluded as not involving an infusion reaction. Three cases involving cardiac arrest were identified as infusion reactions in a subsequent AERS search for ventricular arrhythmias and were moved into the series.

Table 2. Characteristics of Infusion Reaction cases (n=143)

Age (years) [n=97]	Median 65 Range 34 to 84
Gender (n)	Male 95, Female 33
Report Source (n)	U.S. 134, Foreign 9
Report Type (n)	15-Day Expedited 61 Periodic 65 Direct 17
Outcome (n)	Death 4 Life Threatening 46 Hospitalization 29 Other 51

[6] The Warnings section of the labeling states approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines.

- 92% of the infusion reactions occurred with the first dose of treatment.
- 81 cases described the use of prophylactic medications, with diphenhydramine being the most commonly reported.
- There were seven cases of respiratory arrest and seven cases of cardiac arrest. Nine cases reported convulsions, with four of the nine occurring in the context of cardiac or respiratory arrest.
- Of the four deaths, one case involved a cardiorespiratory arrest in a patient with a "Do Not Resuscitate" order and a second case provided minimal information other than anaphylactic shock. The other two cases seemed to involve recurrent reactions after the patient had initially responded to treatment or interruption of the infusion, as described below:

  - ISR# 4530099, 15-Day Report, U.S., December 2004
    A male patient of unknown age with metastatic colorectal cancer received IV diphenhydramine as premedication for his first dose of cetuximab. Ten minutes into the cetuximab infusion, the patient developed pruritus and flushing, a blood pressure of 190/100 and throat discomfort. The infusion was stopped and the patient's symptoms improved. One hour later, he re-developed the same signs as before and also had difficulty swallowing. PO_2 at this time was 82% (sic). The patient was transported by emergency medical services and became less responsive during transit. Intubation was attempted but failed. CPR was administered with cardiotonic agents. In the emergency room, he was found to be without respirations. A transcutaneous pacemaker was inserted and emergency tracheostomy was performed, but the patient expired. The Medical Examiner's report indicated the patient died from anaphylactic shock.
  - ISR# 4513407, Periodic Report, U.S., November 2004
    A male patient of unknown age with colorectal cancer was hospitalized to receive his first dose of cetuximab. No premedications were used. After the infusion was started, he complained of pain. The patient apparently coded shortly afterwards, received CPR, and was intubated. He responded to treatment and was extubated, but then re-coded "within a short time frame." He did not respond to resuscitation. The pathology report noted "pulmonary disease and lysis."

- No clustering of infusion reactions by date of event or lot number was observed, as shown in Figures 1 and 2. Only 37 of the 143 cases reported the associated lot number.

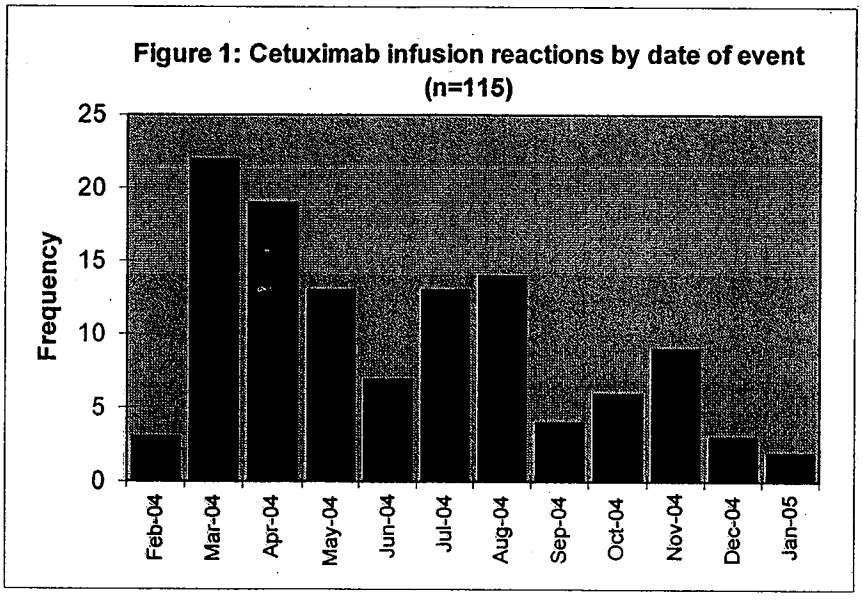
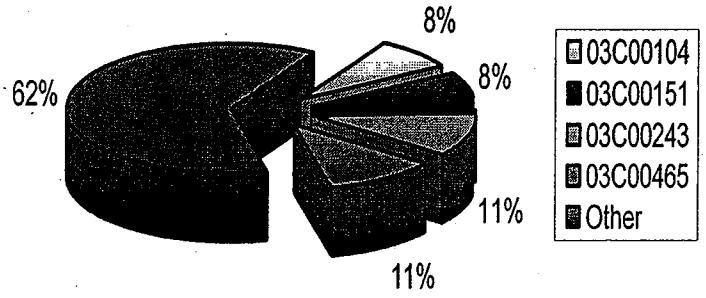


Figure 2: Lot numbers reported for infusion events (n=37)



CONCLUSION

There are reports of infusion reactions involving the unlabeled events of cardiac arrest, respiratory arrest, and convulsions. *In addition, there are two cases that seem to describe recurrent prolonged reactions after the patient initially responded to treatment or interruption of the infusion; one of these cases also refers to a pathology report that noted pulmonary disease with lysis, which might confound interpretation of the event. Consideration should be given to adding a description of these unlabeled postmarketing events in the labeled warning to encourage extended periods of observation/support of patients after presentation with symptoms, as well as requiring the sponsor to update the labeled incidence and outcomes of infusion reactions in the next clinical efficacy supplement.*

SERIOUS AND UNLABELED EVENTS OF INTEREST IN AERS

4. *Hypomagnesemia*

SEARCH AND RESULTS

The AERS database contained 16 unduplicated cases identified with the MedDRA terms hypomagnesaemia (PT) or blood magnesium decreased (PT). One case was excluded as a safety report that occurred three years prior to marketing approval.

Table 2. Characteristics of hypomagnesemia cases (n=15)

Age (years) [n=11]	Median 64 Range 48 to 74
Gender (n)	Male 10, Female 5
Report Source (n)	U.S. 13, Foreign 2
Report Type (n)	15-Day Expedited 14 Periodic 1
Indication (n)	Colorectal cancer 8 Pancreatic cancer 3
Duration of treatment (mos) [n=11]	Median 2 Range 0.8 to 12
Grade of hypomagnesemia[1] [n=11]	Grade 3/4 (n=6) Grade 1/2 (n=5)
Outcome (n)	Death 1 Life threatening 1 Hospitalization 4 Other 8

- The death case involved Grade 1 hypomagnesemia in the setting of febrile neutropenia and hypotension.
- Four cases were potentially confounded by concomitant carboplatin, cisplatin, or zoledronic acid therapy - each of these products describes hypomagnesemia or magnesium loss in the adverse reactions section of the labeling. One other potentially confounded case occurred in a patient with CT evidence of chronic renal tubular injury.
- Although two reports stated cetuximab therapy was discontinued, most reports did not address the issue of drug withdrawal or continuation.
- Nine reports described additional electrolyte abnormalities, such as hypocalcemia or hypokalemia.
- The patients in 9 of the 15 cases required supplemental magnesium therapy. Only three cases described symptoms, such as muscle pain, weakness, or fatigue; however, clinical findings appeared to be incompletely reported across the case series.

An online search of the American Society of Clinical Oncology abstracts revealed a presentation from the 2005 Gastrointestinal Cancers Symposium that described two patients with hypocalcemic crisis and profound hypomagnesemia during cetuximab therapy.[7] The patients experienced numbness and tingling that responded to IV magnesium, but not calcium repletion. Urinalysis showed magnesium wasting. Oral magnesium was insufficient and home IV therapy was required for four weeks following discontinuation of cetuximab. The investigator speculated that cetuximab is inhibiting magnesium reabsorption by interfering with EGFR function in the ascending limb of the loop of Henle (personal communication, Deborah Schrag, Memorial Sloan-Kettering Cancer Center, March 2, 2005).

Two of the most serious clinical consequences of hypomagnesemia include cardiac arrhythmias and seizures. An AERS search was performed for cases of ventricular arrhythmia or sudden death that might describe electrolyte disturbances, including hypomagnesemia. AERS contained 15 non-excluded cases[8] identified with the MedDRA term ventricular arrhythmias and cardiac arrest (HLT). One case of ventricular tachycardia that involved hypokalemia (without mention of the patient's magnesium level) occurred six days after the patient's first dose of cetuximab. No cases related to decreased magnesium levels were identified. AERS was also searched for cases of seizures that might describe electrolyte abnormalities. AERS contained 13 non-excluded cases identified with the MedDRA terms convulsion (PT) and grand mal convulsion (PT).[9] No cases related to decreased magnesium levels were identified.

CONCLUSION

Most cases of hypomagnesemia do not describe serious clinical manifestations. However, magnesium is not routinely monitored in comparison with other electrolytes, so there might be clinically serious events related to hypomagnesemia that were not identified as such. Consideration

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[7] Schrag D, Flombaum C, Chung K, et al. Cetuximab therapy may occasionally cause profound hypomagnesemia and hypocalcemia. Presented at the American Society of Clinical Oncology 2005 Gastrointestinal Cancers Symposium. Orlando, FL. January 27-29, 2005.

[8] One patient developed ventricular trigeminy after receiving six doses of cetuximab; no treatment was ordered and the patient received three additional doses without complications. There were three cases of sudden death that occurred several days after the most recent dose of cetuximab. Ten cases of cardiac arrest or ventricular arrhythmia were experienced in the context of an infusion reaction; none of these cases reported a death outcome.

[9] Nine cases were associated with infusion reactions, with four of the nine occurring in the context of a cardiac or respiratory arrest. One case described seizures in the setting of disabling fatigue and hypercalcemia. One patient with a left parietal brain lesion developed generalized seizures several hours after receiving her third dose of cetuximab. Two other cases provided minimal information.

should be given to routine monitoring of magnesium in patients receiving cetuximab, as well as in clinical situations potentially related to hypomagnesemia.

5. ***Hepatic failure and venoocclusive liver disease***

Cases of hepatic failure or venoocclusive liver disease were selected for review based on the listing of Preferred Terms reported under the Hepatobiliary Disorders SOC.[10] Five unduplicated cases of hepatic failure or venoocclusive liver disease were identified, with one case excluded as a premarketing safety report.

- Two cases involved patients with colorectal cancer who died from hepatic failure related to progression of their metastatic disease.
- There was one case of an anaphylactic infusion reaction in which the patient experienced cardiorespiratory arrest and "shock liver." After hospitalization and intensive treatment, the patient recovered to discharge.
- A 47 year-old male with colorectal cancer and multiple hepatic metastases had received oxaliplatin in combination with various chemotherapy agents for 32 months. The patient was then switched to cetuximab and irinotecan, which he received for almost six months before being hospitalized for bleeding esophageal varices due to portal hypertension. Hepatic biopsy showed perisinusoidal fibrosis, an adverse event that has been associated with oxaliplatin therapy. The report stated it is unknown if the antiangiogenic property of cetuximab could favor the evolution of fibrosis.

Although there is only one possible case of venoocclusive hepatic disease in AERS at this time, we will continue to closely monitor for this event.

6. ***Blood Disorders***

Cases of neutropenia, pancytopenia, and hemolytic anemia were selected for review based on the listing of Preferred Terms reported under the Blood and Lymphatic System Disorders SOC.[11] Of the 31 unduplicated cases reviewed, 28 reported neutropenia or pancytopenia in patients receiving concomitant chemotherapy labeled for such events. There was no obvious evidence of cetuximab augmentation of neutropenia or pancytopenia. There were three cases of hemolytic anemia, as described below:

- A 53 year-old male with metastatic colorectal cancer received cetuximab, oxaliplatin, fluorouracil and folinic acid for seven months before experiencing Grade 2 hemolysis with icterus, a hemoglobin of 8.9 g/dL and bilirubin 6.0 mg/dL. The event completely resolved several weeks later. Hemolysis was considered definitely related to platinum therapy by the investigator.
- A 63 year-old male with colon cancer received three doses of cetuximab and developed possible hemolytic anemia and slight elevation of liver function tests. The patient received a blood transfusion and cetuximab was continued.
- A 58 year-old male experienced autoimmune hemolytic anemia after receiving cetuximab followed by docetaxel for the treatment of an unspecified cancer.

Although these cases do not provide clear evidence of cetuximab causality, we will continue to monitor for hemolytic events associated with cetuximab therapy.

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[10] Hepatic Failure (PT), Venoocclusive Liver Disease (PT)

[11] Anaemia Haemolytic Autoimmune (PT), Haemolysis (PT), Haemolytic Anemia (PT), Neutropenia (PT), Pancytopenia (PT)

7. ***Hemorrhages and intestinal perforations***

Cases of gastrointestinal (GI) and other hemorrhages and intestinal perforations were selected for review based on the listing of Preferred Terms reported under the following SOCs: Gastrointestinal Disorders; Nervous System Disorders; and Respiratory, Thoracic and Mediastinal Disorders.[12] Of the fifteen cases reviewed, three were excluded as premarketing reports. The remaining 12 cases involved eight bleeding events and four cases of intestinal perforation. In two of the four perforation cases, the site was not specified; the other two cases appeared to involve perforations at sites other than the disease locations. One case of GI bleeding provided minimal information and was difficult to evaluate.

Bleeding events

- Three cases of bleeding (GI bleeding; cerebral hemorrhage; and recurrent abdominal wall hematomas) were experienced in patients receiving concomitant warfarin therapy. In two of the three cases, the patient was over-anticoagulated. The third case, which involved recurrent abdominal wall hematomas six months after ventral hernia repair and three months after starting cetuximab, was assessed by the investigator as being related to warfarin.
- One patient developed a cerebral hemorrhage after suffering a head injury and brain contusions in a fall.
- One case of duodenal bleeding occurred in a patient with colorectal cancer who received concomitant bevacizumab and dalteparin, both of which are labeled for bleeding events.
- A 53 year-old male with colorectal cancer, multiple liver metastases, and a history of alcohol-related liver disease developed a duodenal ulcer and recurrent gastrointestinal bleeding after receiving 12 doses of cetuximab. The patient required a transfusion and was treated with pantoprazole.
- A 62 year-old female with metastatic colorectal cancer had received four doses of cetuximab and two doses of irinotecan before developing leukopenia, anemia, and bloody feces. She was hospitalized, transfused, and recovered.[13]

Perforations

- A 57 year-old male with metastatic rectal cancer developed a large bowel obstruction and perforation about two weeks after starting cetuximab and irinotecan therapy. The patient developed peritonitis and septicemia, was placed on palliative care, and expired. The autopsy report recorded a stenosing circumferential carcinoma of the distal rectum, but did not note progressive disease in the rectum or ascending colon, where the bowel had perforated. The investigator assessed the perforation as being possibly related to irinotecan, though the drug is not labeled for that event.
- A male patient of unknown age developed fatal gastrointestinal obstruction and perforation at an unspecified site after receiving two doses of cetuximab and one dose of irinotecan for the treatment of metastatic colorectal cancer. The patient had been treated with nine cycles of bevacizumab prior to starting cetuximab and irinotecan. The physician assessed the obstruction and perforation as being disease-related.
- A 68 year-old female with metastatic colorectal cancer was treated with cetuximab for 2 months and irinotecan for 6 weeks. After receiving 10 days of ciprofloxacin for the treatment of prolonged diarrhea, the patient was hospitalized with abdominal pain and an elevated lipase level. A series of abdominal X-rays showed ileus and perforation of the small bowel (not

[12] Cerebral Haemorrhage (PT), Duodenal Ulcer Haemorrhage (PT), Gastrointestinal Haemorrhage (PT), Gastrointestinal Perforation (PT), Haemoptysis (PT), Intestinal Perforation (PT), Intra-Abdominal Haemorrhage (PT).

[13] The irinotecan labeling describes cases of colitis with ulceration and bleeding.

otherwise specified), for which she had a partial duodenectomy. The patient recovered and was discharged 10 days later.

- A male in his early 40s experienced two bowel perforations at unspecified sites and an abscess after receiving one dose of cetuximab for metastatic colon cancer. The patient was hospitalized.

CONCLUSION

The cases of bleeding events all appear to be confounded and there is no clear signal that associates cetuximab with bowel perforations.

SUMMARY

The main findings of the one-year postmarketing adverse events review include hypomagnesemia and unlabeled manifestations of infusion reactions.

- As magnesium is not routinely monitored in comparison with other electrolytes, there might be clinically serious events related to hypomagnesemia that have not been identified as such. Consideration should be given to routine monitoring of magnesium in patients receiving cetuximab, as well as in clinical situations potentially related to hypomagnesemia.
- There are reports of infusion reactions involving the unlabeled events of cardiac arrest, respiratory arrest, and convulsions. In addition, there are two cases that seem to describe recurrent prolonged reactions after the patient initially responded to treatment or interruption of the infusion. Consideration should be given to clarifying the labeled infusion reaction warnings with this information, as well as requiring the sponsor to update the labeled incidence and outcomes of infusion reactions in the next clinical efficacy supplement

For the purpose of labeling revisions, no appreciable new information was found during review of cases of ILD. The cases of serious skin toxicity appear consistent with the current product labeling, and no case reported the use of doses higher than those recommended in the cetuximab labeling. There is no appreciable new information related to adverse dermatologic reactions in patients receiving or having received radiation therapy.

No clear drug-event associations were apparent during case reviews of hepatic failure, hepatic venoocclusive disease, neutropenia, pancytopenia, hemolytic anemia, gastrointestinal and other hemorrhages, and bowel perforation.

Bob Pratt, Pharm.D.
Safety Evaluator, DDRE

Concur:

Susan Lu, R.Ph.
Team Leader, DDRE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084/S-030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ImClone Systems Incorporated

Bristol-Myers Squibb

September 13, 2005

Re: Important Drug Warning

Dear Healthcare Provider:

ImClone Systems Incorporated and Bristol-Myers Squibb Company are fully committed to assuring timely dissemination of safety information about their products to the healthcare community. We are writing to inform you of changes to the **WARNINGS**, **PRECAUTIONS**, **ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the ERBITUX® (Cetuximab) Prescribing Information.

The **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections have been revised to include language regarding the recommended observation periods following an ERBITUX infusion and in patients who experience infusion reactions.

In addition, the **PRECAUTIONS** and **ADVERSE REACTIONS** sections have been revised to include language regarding an increased incidence of hypomagnesemia seen in ERBITUX clinical trials and recommendations for electrolyte monitoring.

The following changes and additions have been made to the U.S. Package Insert for ERBITUX:

1. The following sentences were added to the Infusion Reactions subsection of the **WARNINGS** section:

   A 1-hour observation period is recommended following the ERBITUX infusion. Longer observation periods may be required in patients who experience infusion reactions.

2. The following sentence was added to the Preparation for Administration subsection of the **DOSAGE AND ADMINISTRATION** section:

   Longer observation periods may be required in those who experience infusion reactions.

3. A new Laboratory Tests: Electrolyte Monitoring subsection has been added to the **PRECAUTIONS** section and contains the following language:

   LABORATORY TESTS: ELECTROLYTE MONITORING

   Patients should be periodically monitored for hypomagnesemia, and accompanying hypocalcemia and hypokalemia, during and following the completion of ERBITUX therapy. Monitoring should continue for a period of time commensurate with the half-life and persistence of the product; i.e., 8 weeks. (See **ADVERSE REACTIONS: Electrolyte Depletion.**)

4. A new Electrolyte Depletion subsection has been added under the **ADVERSE REACTIONS** section and contains the following language:

   ELECTROLYTE DEPLETION

   In 224 patients evaluated in ongoing, controlled clinical trials, the incidence of hypomagnesemia, both overall and severe (NCI-CTC Grades 3 and 4), was increased in patients receiving ERBITUX alone or in combination with chemotherapy as compared to those receiving best supportive care or chemotherapy alone. Approximately one-half of these patients receiving ERBITUX experienced hypomagnesemia and 10-15% experienced severe hypomagnesemia. The onset of electrolyte abnormalities has been reported to occur from days to months after initiation of ERBITUX. Electrolyte repletion was necessary in some patients and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence monitoring after ERBITUX treatment is recommended. (See **PRECAUTIONS: Laboratory Tests**.)

For any questions or to report serious adverse events suspected to be associated with the use of ERBITUX, call **1-888-ERBITUX (372-4889)**. By calling this number, you can speak to a representative directly or use our automated Faxback system to order document code number 2000, which is the Adverse Event Reporting Form. Alternatively this information may be reported to FDA's MedWatch Reporting System by phone at **1-800-FDA-1088**, by facsimile 1-800-FDA-0178, by mail using the Form 3500 at http://www.fda.gov/medwatch/index.html.

Please refer to the accompanying revised full Prescribing Information for ERBITUX, including **boxed WARNING regarding infusion reactions.**

Sincerely,

Eric K. Rowinsky, MD
Senior Vice President, Chief Medical Officer
ImClone Systems Incorporated

A. Collier Smyth, MD
Senior Vice President
Medical Affairs
Bristol-Myers Squibb Company

Final draft
8-10-05

ImClone Systems
Incorporated

33 ImClone Drive
Branchburg, NJ 08876

IMPORTANT DRUG WARNING

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM

Date: August 17, 2005

To: STN BL 125084/30 File

From: Karen D. Jones, CPMS
Division of Biologic Oncology Products
Office of Oncology Drug Products

Subject: July 28, 2005 Communication/ [redacted] b(4)

Participants: FDA/CDER/OND/OODP/DBOP: Lee Pai-Scherf
ImClone Systems, Inc.: Nikhil Mehta

DISCUSSION:

Attached is an email communication between Dr. Lee Pai-Scherf of FDA and Dr. Nikhil Mehta of ImClone Systems, Inc. regarding the supplement STN 125084/30. An agreement was reached to deal with the [redacted] issue in a separate labeling supplement. b(4)

-----Original Message-----
From: Pai-Scherf, Lee
Sent: Thursday, July 28, 2005 9:50 PM
To: 'Nikhil.Mehta@imclone.com'
Cc: Sickafuse, Sharon; Fuchs, Chana
Subject: RE: Revised PI for Erbitux - hypomag discussion

Nik:

Your revised package insert and DHCP are acceptable. b(4)

We would like to move on with this asap. Dr. Keegan suggests that the ——— issue be addressed separately.

Please formally submit the revised PI and DHCP to the sBLA as soon as possible. May be we can finalize this by the end of next week.

Lee
-----Original Message-----
From: Nikhil.Mehta@imclone.com [mailto:Nikhil.Mehta@imclone.com]
Sent: Wednesday, July 27, 2005 10:20 AM
To: lee.pai-scherf@fda.hhs.gov
Subject: Revised PI for Erbitux - hypomag discussion

Hi Lee:

I am attaching the following

1. A table outlining the revisions received from the FDA and proposed revisions by ImClone / BMS (Minus the ——— statement, since this will be reviewed separately). I have included line numbers, however, when sending a Word document, the line numbers may differ slightly depending on the computer/printer. b(4)
2. The proposed Word document showing our revisions to the FDA proposal in track changes.

We plan to send the revised DHCP letter to you later today.

Once you have a chance to review this, pl. advise as to next steps -

Regards

Nik

LICENSING ACTION RECOMMENDATION

Applicant: ImClone Systems, Incorporated **STN:** 125084/30

Product:

Cetuximab

Indication / manufacturer's change:

To revise the WARNINGS and DOSAGE AND ADMINISTRATION sections of the package insert to include information on infusion observation periods and to revise the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert to provide information on hypomagnesemia

■ Approval:
- ☐ Summary Basis For Approval (SBA) included
- ☐ Memo of SBA equivalent reviews included
- ☐ Refusal to File: Memo included
- ☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment ☐ Inspection report included

☐ BiMo inspections completed ☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ☐ Categorical Exclusion

■ Review of labeling Date completed 8-15-05 ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: Lee B. Pai - Chief Date: 9/1/05

Product Office's Responsible Division Director(s)*:

Patricia Keegan Date: 9-1-05

_____ Date: _____

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

☐ Compliance status checked ☐ Acceptable ☐ Hold Date: _____

☐ Cleared from Hold Date: _____

■ Compliance status check Not Required

Regulatory Project Manager (RPM) Sharon Sickafuse Date: 8-15-05
Karen D Jones, CPMS KJ 8-1-05

Responsible Division Director _____ Date: _____
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Thursday, July 07, 2005 4:59 PM
To: 'Nikhil.Mehta@imclone.com'
Subject: PI for STN 125084/30

Attached is the PI with FDA changes marked. The DHCP letter will come in a separate email.

19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

√ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

Sickafuse, Sharon

From: Sickafuse, Sharon
Sent: Monday, July 11, 2005 12:27 PM
To: 'Nikhil.Mehta@imclone.com'
Subject: DHCP letter - FDA changes

STN 125084/30

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

√ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 5, 2005

From: Sharon Sickafuse, CDER/ODE6/DRMP

To: STN 125084/30

Subject: April 27, 2005, teleconference with ImClone regarding the hypomagnesemia CBE supplement

---

Teleconference Date: April 27, 2005

Applicant: ImClone Systems, Inc.

Product: Cetuximab

Approved Use: Treatment of colorectal cancer

Teleconference Purpose: Advise ImClone of the deficiencies in this supplement

Hypomagnesemia Issue:

FDA stated that the CBE supplement submitted on April 7, 2005, contains no clinical data to support the labeling change.

FDA made the following information requests and comments:

1. Please submit the March 18, 2005, amendment to IND 5804 as an amendment to this supplement. Please include patient narratives from all patients in the safety database (investigational and 11 spontaneous post-marketing reports) who experienced hypomagnesemia including the severity of the event, the duration, when it occurred in relationship to time of Cetuximab administration, the treatment received, and the outcome.

2. The revisions to the package insert, as currently proposed, provide insufficient information for health care providers. Please revise the package insert to include the available clinical information regarding hypomagnesemia. This should include information on the severity, the duration, and time to development of

hypomagnesemia in relationship to Cetuximab administration. Information regarding magnesium replacement should also be included in the revised package insert.

3. The DHCP letter, as currently proposed, provides insufficient information for physicians. FDA recommends that ImClone look at the February 24, 2005, action letter from CTEP/NCI on this issue for suggested wording.

ImClone agreed to provide the requested information.

ImClone and FDA agreed that ImClone could print the package insert with the currently proposed wording regarding hypomagnesemia. ImClone will not issue a DHCP letter until the wording has been agreed to with the FDA. ImClone also will not distribute the flash cards to physicians at this time, although FDA stated they could do so as the cards have already been printed and approved by DDMAC.

Late "Anaphylatoid" Reaction Issue:

FDA noted that we've received a few spontaneous post-marketing reports of late "anaphylatoid" reactions and asked ImClone to look at their safety database and consider adding this to the package insert.

ImClone stated that they would like to address this issue in the sBLA for head and neck cancer to be submitted later this year.

FDA disagreed with the proposal. FDA stated that information regarding the potential for late "anaphylatoid" reactions due to Cetuximab administration should be included in the package insert as soon as possible. FDA will provide ImClone with the manufacturer report number of the reports that we received.

ImClone agreed to provide a statement in the package insert as part of the current CBE that cases of late anaphylatoid reactions have been reported.

FDA Attendees:

Center for Drug Evaluation and Research

Office of Drug Evaluation VI
Division of Review Management and Policy
Sharon Sickafuse, M.S.

Division of Therapeutic Biological Oncology Products
Patricia Keegan, M.D.
Lee Pai-Scherf, M.D.

Sponsor Attendees:

ImClone Systems, Inc.

Nikhil Mehta, PhD
Debbie Lynch
Issac Adegbile
Michael Misocky
Hagop Youssoufian, MD

Bristol-Myers Squibb

Ashwin Gollerkeri, M.D.
Steve Knapp
Martin Birkhofer, MD
Savian Nicholas

Merck

Rainer Schmeidl, MD
Frank Raschko, Ph.D.

Attachment: 2 postmarketing reports of late anaphylaxis provided to ImClone by email on April 27th.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ERBITUX safely and effectively. See full prescribing information for ERBITUX.

ERBITUX® (cetuximab)
Solution for intravenous infusion
Initial U.S. Approval: 2004

WARNING: SERIOUS INFUSION REACTIONS and CARDIOPULMONARY ARREST

See full prescribing information for complete boxed warning.

- **Serious infusion reactions, some fatal, occurred in approximately 3% of patients. (5.1)**
- **Cardiopulmonary arrest and/or sudden death occurred in 2% of patients receiving Erbitux in combination with radiation therapy. (5.2, 5.6)**

----------RECENT MAJOR CHANGES----------

Indications and Usage	
Colorectal Cancer (1.2)	07/2009
Warnings and Precautions	
Infusion Reactions (5.1)	09/2008
Dermatologic Toxicity (5.4)	09/2008

----------INDICATIONS AND USAGE----------

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. (1.1, 14.1)
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. (1.1, 14.1)

Colorectal Cancer

- As a single agent, EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens or in patients who are intolerant to irinotecan-based regimens. (1.2, 14.2)
- In combination with irinotecan, EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Approval is based on objective response rate; no data are available demonstrating an improvement in increased survival. (1.2, 14.2)
- Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Erbitux is not recommended for the treatment of colorectal cancer with these mutations. (1.2, 12.1, 14.2)

----------DOSAGE AND ADMINISTRATION----------

- Premedicate with an H_1 antagonist. (2.3)
- Administer 400 mg/m^2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m^2 weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux one week prior to initiation of radiation therapy. (2.1)
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grades 3–4 infusion reactions. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneform rash. Reduce dose for recurrent, severe rash. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- 100 mg/50 mL, single-use vial (3)
- 200 mg/100 mL, single-use vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- **Infusion Reactions:** Immediately stop and permanently discontinue Erbitux for serious infusion reactions. Monitor patients following infusion. (5.1)
- **Cardiopulmonary Arrest:** Closely monitor serum electrolytes during and after Erbitux. (5.2, 5.6)
- **Pulmonary Toxicity:** Interrupt therapy for acute onset or worsening of pulmonary symptoms. (5.3)
- **Dermatologic Toxicity:** Limit sun exposure. Monitor for inflammatory or infectious sequelae. (2.4, 5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 **or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** Administer Erbitux to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Discontinue nursing during and for 60 days following treatment with Erbitux. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

Erbitux® (cetuximab)

Erbitux® (cetuximab) is approved in countries all over the world for treating patients with:

ERI CETUXI

- metastatic colorectal cancer (mCRC) in combination with irinotecan after failure of irinotecan-based therapy
- locally advanced squamous cell carcinoma of the head and neck (SCCHN) in combination with radiation therapy.

Erbitux® is also approved in selected countries for single-agent use in both indications.

Additional links:
www.**erbitux**-international.com[1]

Disclaimer

The information in this section is intended for Healthcare Professionals only.
US residents should consult the EMD Serono, Inc. for information on products approved for sale of America.

Adverse Event Reporting System (AERS)

Standard Report

Line Listing of ISRs with Narrative

Run by: ROBERT PRATT Date - Time: 04/27/2005 - 01:04 pm

Search Criteria:

Manufacturer Type: Sender of ISR

Search Type: ISR
Search for reactions listed: ANY
FDA Rcvd. Date: From:
Reporter Domestic:
Reporter First Name:
Null Values for Country:
Female:
Age Range: From:
MedWatch Source Study:
MedWatch Source Health Professional:
Expedited (15-Day) ISR:
RA Summary ISR:
Include Deactived ISRs:
Non-Serious Outcome:
Event End Date:
OTC Products Only:

Include Concomitant Products:
ISR/Case #: 4530099-
FDA Rcvd. Date: To:
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature:
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products:
Mfr. Control #:
Sort in Descending Order:
Reporter Last Name:
Reporter State:
Male:
Null Gender Values:
Age Range: YEAR
MedWatch Source Consumer:
Periodic ISR:
5 Day ISR:
Follow-up:
Serious Outcome:
Event Start Date:
ReC:

Non-Excluded Product(s) for Selected Active Ingredient(s):

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
Line Listing of ISRs with Narrative

FDA Rcvd. Date	Case	ISR/Best Rep. Ind.	Mfr. Control #	ISR Type	Age	Gender	Country	State	Outcome
Product	**S/C**	**Indication**	**Daily Dose/Unit**	**Route**	**Duration/Unit**	**DeC**	**ReC**	**Lot**	**Dosage Text**
MedDRA Reaction									
Narrative									
12/17/2004	4182708	4530099-3 *	US-BRISTOL-MYERS SQUIBB COMPANY-12655734	Expedited (15-Day)	YR	Male			DE
Erbitux	S	COLORECTAL CANCER METASTATIC		INTRAVENOUS					Loading dose
Benadryl	C	PREMEDICATION		INTRAVENOUS	1 Days				

ANAPHYLACTIC REACTION

A physician reported to a BMS sales representative that a male patient expired sometime after he received a loading dose of cetuximab. The loading dose of cetuximab (indication, dosing and therapy date not provided) was administered at an outpatient infusion center "sometime last week", and the patient expired sometime after receiving the cetuximab. The date and cause of death were not reported. The physician who reported this event to the BMS sales representative was not the patient's physician. Supplemental information received on 10-Aug-2004 from the patient's attending physician reported that the patient expired due to "anaphylactic complications" after receiving the first dose of cetuximab. The first infusion of intravenous (IV) cetuximab was administered on 29-Jul-2004 for the indication of metastatic colorectal cancer, and cetuximab was infused at a rate recommended per the United States Pharmacopoeia insert (USPI) (specific dosing and rate not reported). Approximately 10 minutes into the infusion, the patient started to complain of pruritis and facial flushing. Shortly thereafter, he stated that he had a "lump in his throat". His blood pressure at this time was 190/100. The infusion was then discontinued and fifteen minutes later, the event apparently resolved; the patient received a glass of water and noted the symptoms as greatly improved. One hour later, however, the patient went into the men's room and upon returning, reported the same signs as previously indicated. Additionally, a significant difficulty in swallowing was reported. Partial pressure of oxygen (PO2) at this time was 82 % and the patient's blood pressure was 150/86. Emergency medical services (EMS) were then called. During transit time, the patient became less responsive and upon arrival of EMS, intubation was attempted but failed. Cardiopulmonary resuscitation (CPR) was subsequently administered in conjunction with unspecified cardiotonic agents. The patient was transported to the emergency room (ER) at a nearby hospital where he was found to be without respirations. Consequently, a transcutaneous pacemaker was inserted and an emergent tracheostomy was performed. Unfortunately, all of these actions were of no avail and the patient expired, per the reporter, due to anaphylactic complications. The patient had been experiencing dyspnea for a duration of one week prior to the administration of cetuximab. He had no allergies and was negative for medical history aside from Stage 4 colorectal cancer with disease progression to the pelvis and lungs bilaterally. Supplemental information was received on 19-Oct-2004 from the Food and Drug Administration (FDA): A physician (forensic pathologist) from a Medical Examiners Office reported to the FDA Central Triage Unit (sequence number 228403E) that a male patient expired due to an acute anaphylactic reaction following a cetuximab infusion. Therapy with intravenous (IV) cetuximab was administered for the first time on [redacted] for the indication of metastatic colon cancer. Autopsy and microscopic examination were performed (results not provided). Additional information was received on 21-Oct-2004 from a nurse at the office of the initial reporting physician. The nurse confirmed that the male patient had a weight of 295 pounds and that cetuximab had been administered on [redacted], not 29-Jul-2004 as had initially been reported. The date of death was confirmed as [redacted]. Supplemental information received on 10-Dec-2004 by an ImClone sales representative from a pharmacist at the clinic reported that the patient had received diphenhydramine IV as a premedication and that the patient had received about 1/4 of the cetuximab infusion when he went into anaphylactic shock. The paramedics responded within 9 minutes, but the patient had expired before they arrived.

Adverse Event Reporting System (AERS)

Standard Report

Line Listing of ISRs with Narrative

Run by: ROBERT PRATT Date - Time: 04/27/2005 - 01:07 pm

Search Criteria:

Manufacturer Type: Sender of ISR

Search Type: ISR
Search for reactions listed: ANY
FDA Rcvd. Date: From:
Reporter Domestic:
Reporter First Name:
Null Values for Country:
Female:
Age Range: From:
MedWatch Source Study:
MedWatch Source Health Professional:
Expedited (15-Day) ISR:
RA Summary ISR:
Include Deactived ISRs:
Non-Serious Outcome:
Event End Date:
OTC Products Only:

Include Concomitant Products:
ISR/Case #: 4513407-
FDA Rcvd. Date: To:
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature:
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products:
Mfr. Control #:
Sort in Descending Order:
Reporter Last Name:
Reporter State:
Male:
Null Gender Values:
Age Range: YEAR
MedWatch Source Consumer:
Periodic ISR:
5 Day ISR:
Follow-up:
Serious Outcome:
Event Start Date:
ReC:

Non-Excluded Product(s) for Selected Active Ingredient(s):

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
Line Listing of ISRs with Narrative

FDA Rcvd. Date	Case	ISR/Best Rep. Ind.	Mfr. Control #	ISR Type	Age	Gender	Country	State	Outcome
Product	S/C	Indication	Daily Dose/Unit	Route	Duration/Unit	DeC	ReC	Lot	Dosage Text
MedDRA Reaction									
Narrative									
11/30/2004	5685153	4513407-9 *	US-BRISTOL-MYERS SQUIBB COMPANY-12704862	Periodic	YR	Male			DE
Erbitux	S			INTRAVENOUS					Initial infusion
ANAPHYLACTIC SHOCK		PAIN							

An oncology registered nurse reported to a BMS oncology representative that a male patient (age not provided) developed anaphylactic shock and died after receiving intravenous cetuximab. The patient was hospitalized for an undisclosed diagnosis and he received a cetuximab treatment. The reporter was not sure if this was the patient's initial treatment with cetuximab (dosing not reported). Reportedly, per the instruction of patient's oncologist, no any premedication was given prior to the cetuximab administration. During the infusion, the patient developed anaphylactic shock. The treatment was stopped, and the patient remained in the hospital where he passed away a day or so later. Supplemental information received on 11-Oct-2004 by a BMS Oncology Medical Liaison from an oncology nurse attending an "Erbitux CORE presentation" reported that the patient had been placed in the hospital for the initial cetuximab infusion by one of the local medical oncologists. The patient was a "colorectal patient". No pre-medications were administered prior to the cetuximab infusion. The nurse relates that the infusion was started and the patient complained of pain. She left the room to obtain pain medication. She was out of the room retrieving pain medication when the patient's daughter ran into the hall calling for help. Emergency medical management and cardiopulmonary resuscitation (CPR) were administered along with endotracheal intubation. The patient responded to treatment, was awake, began talking and was extubated. Within a short time frame the patient arrested again and did not respond to a second resuscitation attempt. The nurse reported that the pathologist stated that there was significant pulmonary disease and lysis noted.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

APR 14 2005

ImClone Systems, Incorporated
Attention: Nikhil Mehta, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
33 ImClone Drive
Branchburg, NJ 08876

Dear Dr. Mehta:

SUBMISSION TRACKING NUMBER (STN) BL 125084/30 has been assigned to your recent supplement to your biologics license application for Cetuximab received on April 11, 2005, to revise the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert to provide information on hypomagnesemia.

This acknowledgment recognizes that your submission is in the form of a "**Special Labeling Supplement--Changes Being Effected**" as described under 21 CFR 601.12(f)(2). Continued use of the changes is subject to final approval of this supplement.

Unless we notify you within 60 days of the receipt date that the supplement is not sufficiently complete to permit substantive review, this supplement will be considered filed.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Sharon Sickafuse, at (301) 827-5101.

Sincerely,

Earl Dye

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Acknowledgment/Filing (AFL)
Summary Text: (CBE)

SS & RIS Data Check:

- **If "Unacceptable for Filing" add 2nd LETTER TYPE "UN".**
- **Communication**

RIS Data Check:

- **Submission Screen: In Arrears Box Is Checked**
- **Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match**
- **No Action Due Date**
- **STN Status – Unacceptable for Filing**

cc: HFD-109/Sharon Sickafuse
HFD-107/Lee Pai-Scherf
HFD-141/Ayoub Suliman
DRMP BLA file (hard copy)

History: K. Townsend: 4.13.2005

File Name: S:\STN 2005\125084.30.CBE.doc

Division	Name/Signature	Date
DRMP	Sickafuse	4-13-05
ODE VI/DRMP	Karen D Jane	4-13-05
DRMP	Dye	4-14-05
DRMP	Kelly Simmons	4/15/05

ImClone Systems Incorporated

33 Chubb Way
Branchburg, NJ 08876
Tel: (908) 218-9588
Fax: (908) 704-8325
www.imclone.com

VIA COURIER

Biologics License Application –ERBITUX®
(Cetuximab) STN BL 125084

Re: Supplement – Changes Being Effected (CBE)

April 7, 2005

Karen Weiss, MD
CDER Office of New Drugs
Office of Drug Evaluation VI
CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Dear Dr. Weiss:

Reference is made to our Biologics License Application for ERBITUX® (STN BL 125084). We are hereby submitting, in duplicate, a Changes Being Effected (CBE) Supplement to the BLA.

This supplement is being provided as a follow-up to BB IND 5804, Serial Number 627, submitted to FDA on March 18, 2005 which included the response to FDA's request for information regarding our investigation of the cases of Hypomagnesemia.

This CBE supplement contains:

- A revised package insert (PI) including information related to our investigation of the cases of Hypomagnesemia in both Adobe Acrobat (.pdf) and Microsoft Word (.doc) formats. Additionally, a strikethrough version of the PI identifying, with particularity, the revisions included in this supplement.

- A communication plan of action regarding Cetuximab Therapy and Hypomagnesemia.

This amendment is comprised of one CD provided in duplicate. The electronic data on this disk has been checked for viruses using Symantec Anti-Virus, Corporate Edition, Version 8.1 and determined to be virus free.

If you have any questions or concerns regarding this submission, please contact me by telephone at (908) 541-8137 or by facsimile at (908) 218-0555.

Sincerely,

Nikhil Mehta, Ph.D.
Vice President,
Regulatory Affairs and Quality Assurance

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ImClone Systems Incorporated	April 7, 2005 APR 11 2005
TELEPHONE NO. *(Include Area Code)*	FACSIMILE *(FAX)* Number *(Include Area Code)*
908-541-8137	908-218-0555
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 33 ImClone Drive, Branchburg, New Jersey 08876	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* STN BL 125084

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Cetuximab	ERBITUX ®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
	IMC-C225

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Liquid	100 mg/vial	Intravenous Injection

(PROPOSED) INDICATION(S) FOR USE: ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☒ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☒ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 CD THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☑ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Previously Provided

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Previously Provided

This application contains the following items: *(Check all that apply)*

☐	1. Index
☒	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Hypomagnesemia Communication Plan of Action

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Nikhil Mehta	Nikhil Mehta, VP Regulatory Affairs and QA	4/7/2005

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
33 ImClone Drive, Branchburg, New Jersey 08876	(908) 541-8137

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Food and Drug Administration
CDER, HFD-99
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Rockville, MD 20852-1448

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