DÉPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125084/1

JUN 18 2004

ImClone Systems, Incorporated
Attention: Lily W. Lee, Ph.D.
Vice President, Regulatory Affairs and Biostatistics
33 Chubb Way
Branchburg, NJ 08876-3904

Dear Dr. Lee:

Your request to supplement your biologics license application for Cetuximab to include the Branchburg, NJ facility (BB36) as an additional site for manufacture of Cetuximab drug substance and to update the package insert with safety data obtained using BB36 Cetuximab drug substance has been approved.

Please submit results of ongoing stability studies by August 1, 2005.

We acknowledge your June 15, 2004, written commitment as outlined below:

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70:

To submit additional stability data on drug substance and drug product stressed by agitation representative of shipping under worst case conditions by July 30, 2004.

Submit the final study report to your BLA STN BL 125084/0. Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing study commitment as appropriate:

- Postmarketing Study Final Report
- Postmarketing Study Correspondence

Please submit 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).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

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

Sincerely,

(b)(6)

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

Enclosure: Package Insert Labeling

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
Summary Text: Manuf. Supplmt. Other
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: DRMP BLA file
HFM-500/K. Weiss
HFM-561/S. Kozlowski
HFM-555/P. Swann
HFM-110/RIMS
HFM-555/C. Fuchs
HFM-585/E. Dye
HFM-588/S. Sickafuse
HFD-328/M. Swider
HFM-570/P. Keegan
HFM-579/L. Pai-Scherf
HFD-013/D. Taub (ORP/DIDP)
HFD-013/H. Brubaker (ORP/DIDP)
HFD-328/TFRB Blue file/M. Smedley
HFD-320/J. Farmulare
HFD-322/E. Rivera-Martinez, IPCB
HFD-42/M. Kiester

History: Sickafuse:5-19-04:6-14-04:6-15-04: K. Townsend: 6.16.2004:sks:6-17-04: K. Townsend: 6.17.2004

File Name:(S: Sickafuse\Cetuximab\BB36\approval letter.doc)

(b)(6)

[redacted]

Final Draft Label
6-10-04

ERBITUX™

Rx only

(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, 0.42 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

	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI[a])	
Populations	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.

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**.)

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. Since human IgG1 is secreted in human milk, the potential for absorption and harm to the infant after ingestion is unknown. 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

	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=420)	
Body System Preferred Term[1]	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

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			
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
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.

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.**

ERBITUX CAN 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.

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 trademark of ImClone Systems Incorporated.

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

xxxxxxxxx

Revised _____