CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125084Orig1s277, s280

Trade Name:	ERBITUX
Generic or Proper Name:	cetuximab
Sponsor:	Eli Lilly and Company
Approval Date:	April 6, 2021
Indication:	Head and Neck Cancer • Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy • Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil • Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy Colorectal Cancer K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test • in combination with FOLFIRI for first-line treatment, • in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, • as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan

CENTER FOR DRUG EVALUATION AND RESEARCH

125084Orig1s277, s280

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	**X**
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

125084Orig1s277, s280

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	**X**
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084Orig1s277, s280

APPROVAL LETTER

BLA 125084/S-277
BLA 125084/S-280

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Susan Holsmer-Brand, M.Sc.
Consultant, Global Regulatory Affairs - NA
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Mrs. Holsmer-Brand:

Please refer to your supplemental biologics license application (sBLA), dated and received November 19, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for ERBITUX (cetuximab) injection, for intravenous use.

This Prior Approval sBLA provides for an alternate cetuximab biweekly dosage regimen for the approved indications in patients with K-Ras wild-type, EGFR-expressing metastatic colorectal cancer (S-277) or squamous cell carcinoma of the head and neck (S-280), when used as a single agent or in combination with chemotherapy, as reflected in subsections 2.1 and 2.2 of the DOSAGE AND ADMINISTRATION section of ERBITUX product labeling.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information)

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement in colorectal cancer because necessary studies are impossible or highly impracticable due to the extreme rarity of this disease in pediatric patients.

Because this drug product for the treatment of squamous cell cancer of the head and neck indication has an orphan drug designation, you are exempt from this requirement for this indication.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Maryam Khazraee, Regulatory Health Project Manager, at 301-796-7119.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA B DONOGHUE
04/06/2021 02:08:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084Orig1s277, s280

LABELING

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) injection, for intravenous use
Initial U.S. Approval: 2004

WARNING: INFUSION REACTIONS and CARDIOPULMONARY ARREST

See full prescribing information for complete boxed warning.

- **ERBITUX can cause serious and fatal infusion reactions. (5.1, 6) Immediately interrupt and permanently discontinue ERBITUX for serious infusion reactions. (2.4)**
- **Cardiopulmonary arrest or sudden death occurred in patients with squamous cell carcinoma of the head and neck receiving ERBITUX with radiation therapy or with a cetuximab product with platinum-based therapy and fluorouracil. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX administration. (5.2, 5.6)**

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

Dosage and Administration

Recommended Dosage for Squamous Cell Carcinoma of the Head and Neck (SCCHN) (2.1)	04/2021
Recommended Dosage for Colorectal Cancer (CRC) (2.2)	04/2021
Warnings and Precautions, Infusion Reactions (5.1)	11/2020

----------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 locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil. (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

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. (1.2, 5.7, 12.1, 14.2)

Limitations of Use: ERBITUX is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown. (5.7)

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

- Premedicate with an H_1 receptor antagonist. (2.3)
- In Combination With Radiation Therapy:
  - Initial dose: 400 mg/m^2 administered as a 120-minute intravenous infusion one week prior to initiating a course of radiation therapy. (2.1)
  - Subsequent doses: 250 mg/m^2 administered as a 60-minute infusion every week for the duration of radiation therapy (6–7 weeks). (2.1)
  - Complete ERBITUX administration 1 hour prior to radiation therapy. (2.1)
- As Single-Agent or in Combination With Chemotherapy
  - Weekly: Administer initial dose of 400 mg/m^2 as a 120-minute intravenous infusion, and subsequent doses of 250 mg/m^2 infused over 60 minutes once weekly. (2.1, 2.2)
  - Biweekly: Administer 500 mg/m^2 as a 120-minute intravenous infusion every two weeks. (2.1, 2.2)
  - Complete ERBITUX administration 1 hour prior to chemotherapy. Continue treatment until disease progression or unacceptable toxicity (2.1, 2.2)
- See full prescr bing information for dosage adjustments for adverse reactions. (2.4)

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

- Injection: 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL (2 mg/mL) in a single-dose vial. (3)

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

None. (4)

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

- Infusion Reactions: Monitor patients following infusion. Immediately stop and permanently discontinue ERBITUX for serious infusion reactions. (2.4, 5.1)
- Cardiopulmonary Arrest: Monitor serum electrolytes during and after ERBITUX. (5.2, 5.6)
- Pulmonary Toxicity: Interrupt or permanently discontinue for acute onset or worsening of pulmonary symptoms. (2.4, 5.3)
- Dermatologic Toxicity: Monitor for dermatologic toxicities or infectious sequelae. Limit sun exposure. (2.4, 5.4)
- Hypomagnesemia and Accompanying Electrolyte Abnormalities: Monitor during treatment and for at least 8 weeks following the completion. Replete electrolytes as necessary. (5.6)
- Increased tumor progression, increased mortality, or lack of benefit observed in patients with Ras-mutant mCRC. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception. (5.8, 8.1, 8.3)

----------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 Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: INFUSION REACTIONS and CARDIOPULMONARY ARREST

Infusion Reactions: ERBITUX can cause serious and fatal infusion reactions *[see Warnings and Precautions (5.1), Adverse Reactions (6)]*. Immediately interrupt and permanently discontinue ERBITUX for serious infusion reactions *[see Dosage and Administration (2.4)]*.

Cardiopulmonary Arrest: Cardiopulmonary arrest or sudden death occurred in patients with squamous cell carcinoma of the head and neck receiving ERBITUX with radiation therapy or a cetuximab product with platinum-based therapy and fluorouracil. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX administration *[see Warnings and Precautions (5.2, 5.6)]*.

1 INDICATIONS AND USAGE

1.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

ERBITUX® is indicated:

- in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN).
- in combination with platinum-based therapy with fluorouracil for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN.
- as a single-agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer (CRC)

ERBITUX is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test *[see Dosage and Administration (2.2)]*:

- in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single-agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: ERBITUX is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown *[see Warnings and Precautions (5.7)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Squamous Cell Carcinoma of the Head and Neck (SCCHN)

In combination with radiation therapy

- Initial dose: 400 mg/m^2 administered as a 120-minute intravenous infusion one week prior to initiating a course of radiation therapy.
- Subsequent doses: 250 mg/m^2 administered as a 60-minute infusion every week for the duration of radiation therapy (6–7 weeks).
- Complete ERBITUX administration 1 hour prior to radiation therapy.

As a single-agent or in combination with platinum-based therapy and fluorouracil

Administer Erbitux as a single-agent or in combination with platinum-based therapy and fluorouracil on a weekly or biweekly schedule.

Weekly Dosage

- Initial dose: 400 mg/m^2 administered as a 120-minute intravenous infusion
- Subsequent doses: 250 mg/m^2 administered as a 60-minute infusion every week

Biweekly Dosage

- Initial and subsequent doses: 500 mg/m^2 administered as a 120-minute intravenous infusion every 2 weeks

Complete ERBITUX administration 1 hour prior to platinum-based therapy with fluorouracil. Continue treatment until disease progression or unacceptable toxicity.

2.2 Recommended Dosage for Colorectal Cancer (CRC)

Determine EGFR-expression status using FDA-approved tests prior to initiating treatment. Also confirm the absence of a Ras mutation prior to initiation of treatment with ERBITUX. Information on FDA-approved tests for the detection of K-Ras mutations in patients with metastatic CRC is available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm.

As a single-agent or in combination with irinotecan or FOLFIRI (irinotecan, fluorouracil, leucovorin)

Administer Erbitux as a single-agent or in combination with irinotecan or FOLFIRI (irinotecan, fluorouracil, leucovorin) on a weekly or biweekly schedule.

Weekly Dosage

- Initial dose: 400 mg/m^2 administered as a 120-minute intravenous infusion
- Subsequent doses: 250 mg/m^2 administered as a 60-minute infusion every week

Biweekly Dosage

- Initial and subsequent doses: 500 mg/m^2 administered as a 120-minute intravenous infusion every 2 weeks

Complete ERBITUX administration 1 hour prior to irinotecan or FOLFIRI. Continue treatment until disease progression or unacceptable toxicity.

2.3 Premedication

Premedicate with a histamine-1 (H_1) receptor antagonist intravenously 30–60 minutes prior to the first dose or subsequent doses as deemed necessary *[see Warnings and Precautions (5.1)]*.

2.4 Dosage Modifications for Adverse Reactions

Reduce, delay, or discontinue ERBITUX to manage adverse reactions as described in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Infusion reactions *[see Warnings and Precautions (5.1)]*	Grade 1 or 2	Reduce the infusion rate by 50%.
	Grade 3 or 4	Immediately and permanently, discontinue ERBITUX.
Dermatologic toxicities and infectious sequelae (e.g., acneiform rash, mucocutaneous disease) *[see Warnings and Precautions (5.4)]*	1st occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 250 mg/m^2. If no improvement, discontinue ERBITUX.
	2nd occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 200 mg/m^2. If no improvement, discontinue ERBITUX.
	3rd occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 150 mg/m^2. If no improvement, discontinue ERBITUX.
	4th occurrence; Grade 3 or 4	Discontinue ERBITUX.
Pulmonary toxicity *[see Warnings and Precautions (5.3)]*	Acute onset or worsening pulmonary symptoms	Delay infusion 1 to 2 weeks; if condition improves, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks or interstitial lung disease (ILD) is confirmed, discontinue ERBITUX.

[a] National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 2.0.

2.5 Preparation for Administration

- 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.
- Visually inspect for foreign particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is discolored, cloudy, or contains foreign particulate matter.
- Do not administer ERBITUX as an intravenous push or bolus.
- Administer via infusion pump or syringe pump. Do not exceed an infusion rate of 10 mg/min.
- Administer through a low protein binding 0.22-micrometer in-line filter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL (2 mg/mL) as a clear, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

ERBITUX can cause serious and fatal infusion reactions. Infusion reactions of any grade occurred in 8.4% of 1373 patients who received ERBITUX across clinical trials. Severe (Grades 3 and 4) infusion reactions occurred in 2.2% of patients *[see Adverse Reactions (6.1)]*. Signs and symptoms included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest.

The risk of anaphylactic reactions may be increased in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-α-1,3-galactose (alpha-gal). Consider testing patients for alpha-gal IgE antibodies using FDA-cleared methods prior to initiating ERBITUX. Negative results for alpha-gal antibodies do not rule out the risk of severe infusion reactions.

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines. Infusion reactions may occur during or several hours following completion of the infusion.

Premedicate with a histamine-1(H_1) receptor antagonist as recommended *[see Dosage and Administration (2.3)]*. Monitor patients for at least 1 hour following each ERBITUX infusion, in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. In patients requiring treatment for infusion reactions, monitor for more than 1 hour to confirm resolution of the reaction. Interrupt the infusion and upon recovery, resume the infusion at a slower rate or permanently discontinue ERBITUX based on severity *[see Dosage and Administration (2.4)]*.

5.2 Cardiopulmonary Arrest

ERBITUX can cause cardiopulmonary arrest. Cardiopulmonary arrest or sudden death occurred in 2% of 208 patients treated with radiation therapy and ERBITUX in BONNER. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of ERBITUX. One patient with no prior history of coronary artery disease died one day after the last dose of ERBITUX.

In EXTREME, fatal cardiac disorders and/or sudden death occurred in 3% of 219 patients treated with a cetuximab product in combination with platinum-based therapy and fluorouracil.

Carefully consider use of ERBITUX with radiation therapy or platinum-based therapy with fluorouracil in patients with SCCHN with a history of coronary artery disease, congestive heart failure, or arrhythmias. Monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after ERBITUX *[see Warnings and Precautions (5.6)]*.

5.3 Pulmonary Toxicity

ERBITUX can cause interstitial lung disease (ILD). ILD, including 1 fatality, occurred in <0.5% of 1570 patients receiving ERBITUX in clinical trials.

Monitor patients for signs and symptoms of pulmonary toxicity. Interrupt or permanently discontinue ERBITUX for acute onset or worsening of pulmonary symptoms. Permanently discontinue ERBITUX for confirmed ILD *[see Dosage and Administration (2.4)]*.

5.4 Dermatologic Toxicity

ERBITUX can cause dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis.

Acneiform rash occurred in 82% of the 1373 patients who received ERBITUX across clinical trials. Severe (Grades 3 or 4) acneiform rash occurred in 9.7% of patients *[see Adverse Reactions (6.1)].* Acneiform rash usually developed within the first two weeks of therapy; the rash lasted more than 28 days after stopping ERBITUX in most patients.

Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing, has been observed in patients who received ERBITUX. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis).

Monitor patients receiving ERBITUX for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during ERBITUX therapy. Withhold, reduce dose or permanently discontinue ERBITUX based on severity of acneiform rash or mucocutaneous disease *[see Dosage and Administration (2.4)]*.

5.5 Risks Associated with Use in Combination with Radiation and Cisplatin

In a controlled study, 940 patients with locally advanced SCCHN were randomized 1:1 to receive either ERBITUX in combination with radiation therapy and cisplatin or radiation therapy and cisplatin alone. The addition of ERBITUX resulted in an increase in the incidence of Grade 3 and 4 mucositis, radiation recall syndrome, acneiform rash, cardiac events, and electrolyte disturbances compared to radiation and cisplatin alone. Adverse reactions with fatal outcome were reported in 4% of patients in the ERBITUX combination arm and 3% in the control arm. In the ERBITUX arm, 2% experienced myocardial ischemia compared to 0.9% in the control arm. The main efficacy outcome of the study was progression-free survival (PFS). The addition of ERBITUX to radiation and cisplatin did not improve PFS. ERBITUX is not indicated for the treatment of SCCHN in combination with radiation and cisplatin.

5.6 Hypomagnesemia and Accompanying Electrolyte Abnormalities

ERBITUX can cause hypomagnesemia. Hypomagnesemia occurred in 55% of 365 patients receiving ERBITUX in Study CA225-025 and two other clinical trials in patients with colorectal cancer (CRC) or head and neck cancer, including Grades 3 and 4 in 6% to 17%.

In EXTREME, where a cetuximab product was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and fluorouracil resulted in an increased incidence of hypomagnesemia of any grade (14%) and of Grade 3 or 4 hypomagnesemia (7%). Hypomagnesemia of any grade occurred in 4% of patients who received cetuximab, carboplatin, and fluorouracil. No patient experienced Grade 3 or 4 hypomagnesemia *[see Adverse Reactions (6.1)].*

Hypomagnesemia and accompanying electrolyte abnormalities can occur days to months after initiating ERBITUX. Monitor patients weekly during treatment for hypomagnesemia, hypocalcemia, and hypokalemia, and for at least 8 weeks following the completion of ERBITUX. Replete electrolytes as necessary.

5.7 Increased Tumor Progression, Increased Mortality, or Lack of Benefit in Patients with Ras-Mutant mCRC

ERBITUX is not indicated for the treatment of patients with CRC that harbor somatic mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either K-Ras or N-Ras and hereafter is referred to as “Ras” or when the Ras status is unknown.

Retrospective subset analyses of Ras-mutant and wild-type populations across several randomized clinical trials, including CRYSTAL, were conducted to investigate the role of Ras mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies. Use of cetuximab in patients with Ras mutations resulted in no clinical benefit with treatment related toxicity. Confirm Ras mutation status in tumor specimens prior to initiating ERBITUX *[see Indications and Usage (1.2)]*.

5.8 Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, ERBITUX can cause fetal harm when administered to a pregnant woman. There are no available data for ERBITUX exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryolethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ERBITUX and for 2 months after the last dose of ERBITUX *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Infusion reactions *[see Warnings and Precautions (5.1)]*.
- Cardiopulmonary arrest *[see Warnings and Precautions (5.2)]*.
- Pulmonary toxicity *[see Warnings and Precautions (5.3)]*.
- Dermatologic toxicity *[see Warnings and Precautions (5.4)]*.
- Hypomagnesemia and Electrolyte Abnormalities *[see Warnings and Precautions (5.6)]*.

6.1 Clinical Trials Experience

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 data described in Warnings and Precautions reflect exposure to ERBITUX in 1373 patients with SCCHN or CRC enrolled in clinical trials and treated at the recommended dosage for a median of 7 to 14 weeks *[see Clinical Studies (14)]*.

The most common adverse reactions in ERBITUX clinical trials (incidence ≥25%) include cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

In Combination with Radiation Therapy

The safety of ERBITUX in combination with radiation therapy compared to radiation therapy alone was evaluated in BONNER. The data described below reflect exposure to ERBITUX in 420 patients with locally or regionally advanced

SCCHN. ERBITUX was administered at the recommended dosage (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 8 infusions (range 1 to 11) *[see Clinical Studies (14.1)]*.

Table 2 provides the frequency and severity of adverse reactions in BONNER.

Table 2: Selected Adverse Reactions in ≥10% of Patients with Locoregionally Advanced SCCHN (BONNER)[a]

Adverse Reaction	ERBITUX with Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
General				
Asthenia	56	4	49	5
Fever[c]	29	1	13	1
Headache	19	<1	8	<1
Chills[c]	16	0	5	0
Infusion Reaction[d]	15	3	2	0
Infection	13	1	9	1
Gastrointestinal				
Nausea	49	2	37	2
Emesis	29	2	23	4
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolism and Nutrition				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Increased Alanine Transaminase[e]	43	2	21	1
Increased Aspartate Transaminase[e]	38	1	24	1
Increased Alkaline Phosphatase[e]	33	<1	24	0
Respiratory				
Pharyngitis	26	3	19	4
Dermatologic				
Acneiform Rash[f]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[a] Adverse reactions occurring in ≥10% of patients in the ERBITUX combination arm and at a higher incidence (≥5%) compared to the radiation alone arm.

[b] Adverse reactions were graded using the NCI CTC, version 2.0.

[c] Includes cases also reported as infusion reaction.

[d] Infusion reaction 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”.

[e] Based on laboratory measurements, not on reported adverse reactions, the number of subjects with tested samples varied from 205–206 for ERBITUX with Radiation arm; 209–210 for Radiation alone.

[f] Acneiform rash defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

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

In Combination with Platinum-based Therapy and Fluorouracil

The safety of a cetuximab product in combination with platinum-based therapy and fluorouracil or platinum-based therapy and fluorouracil alone was evaluated in EXTREME. The data described below reflect exposure to a cetuximab product in 434 patients with recurrent locoregional disease or metastatic SCCHN. Because ERBITUX provides approximately 22% higher exposure relative to the cetuximab product, the data provided below may underestimate the incidence and severity of adverse reactions anticipated with ERBITUX for this indication; however, the tolerability of the recommended dose is supported by safety data from additional studies of ERBITUX *[see Clinical Pharmacology (12.3)]*. Cetuximab was administered intravenously at a dosage of 400 mg/m^2 for the initial dose, followed by 250 mg/m^2 weekly. Patients received a median of 17 infusions (range 1 to 89) *[see Clinical Studies (14.1)]*.

Table 3 provides the frequency and severity of adverse reactions in EXTREME.

Table 3: Selected Adverse Reactions in ≥10% of Patients with Recurrent Locoregional Disease or Metastatic SCCHN (EXTREME)[a]

Adverse Reaction	Cetuximab with Platinum-based Therapy and fluorouracil (n=219)		Platinum-based Therapy and fluorouracil Alone (n=215)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
Eye				
Conjunctivitis	10	0	0	0
Gastrointestinal				
Nausea	54	4	47	4
Diarrhea	26	5	16	1
General and Administration Site				
Pyrexia	22	0	13	1
Infusion Reaction[c]	10	2	<1	0
Infections				
Infection[d]	44	11	27	8
Metabolism and Nutrition				
Anorexia	25	5	14	1
Hypocalcemia	12	4	5	1
Hypokalemia	12	7	7	5
Hypomagnesemia	11	5	5	1
Dermatologic				
Acneiform Rash[e]	70	9	2	0
Rash	28	5	2	0
Acne	22	2	0	0
Dermatitis Acneiform	15	2	0	0
Dry Skin	14	0	<1	0
Alopecia	12	0	7	0

[a] Adverse reactions occurring in ≥10% of patients in the cetuximab combination arm and at a higher incidence (≥5%) compared to the platinum-based therapy and fluorouracil alone arm.

[b] Adverse reactions were graded using the NCI CTC, version 2.0.

[c] Infusion reaction defined as “anaphylactic reaction”, “hypersensitivity”, “fever and/or chills”, “dyspnea”, or “pyrexia” on the first day of dosing.

[d] Infection excludes sepsis-related events which are presented separately.

[e] Acneiform rash defined as “acne”, “dermatitis acneiform”, “dry skin”, “exfoliative rash”, “rash”, “rash erythematous”, “rash macular”, “rash papular”, or “rash pustular”.

Chemotherapy = cisplatin and fluorouracil or carboplatin and fluorouracil

For cardiac disorders, approximately 9% of patients in both treatment arms in EXTREME experienced a cardiac event. The majority of these events occurred in patients who received cisplatin and fluorouracil with or without cetuximab. Cardiac disorders were observed in 11% and 12% of patients who received cisplatin and fluorouracil with or without cetuximab, respectively, and 6% and 4% in patients who received carboplatin and fluorouracil with or without cetuximab, respectively. In both arms, the incidence of cardiovascular events was higher in the cisplatin and fluorouracil containing subgroup. Death attributed to cardiovascular events or sudden death was reported in 3% of the patients in the cetuximab with platinum-based therapy and fluorouracil arm and in 2% of the patients in the platinum-based therapy and fluorouracil alone arm.

K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (mCRC)

In Combination with FOLFIRI

The safety of a cetuximab product in combination with FOLFIRI or FOLFIRI alone was evaluated in CRYSTAL. The data described below reflect exposure to a cetuximab product in 667 patients with K-Ras wild-type, EGFR-expressing, mCRC. ERBITUX provides approximately 22% higher exposure compared to this product; however, the safety data from CRYSTAL is consistent in incidence and severity of adverse reactions with those seen for ERBITUX in this indication. Cetuximab was administered intravenously at a dosage of 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly. Patients received a median of 24 infusions (range 1 to 224) *[see Clinical Studies (14.2)]*.

Serious adverse reactions included pulmonary embolism, which was reported in 4.4% of patients treated with cetuximab with FOLFIRI as compared to 3.4% of patients treated with FOLFIRI alone.

Table 4 provides the frequency and severity of adverse reactions in CRYSTAL.

Table 4: Selected Adverse Reactions in ≥10% of Patients with K-Ras Wild-type and EGFR-expressing, Metastatic Colorectal Cancer (CRYSTAL)[a]

Adverse Reaction	Cetuximab with FOLFIRI (n=317)		FOLFIRI Alone (n=350)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
Hematologic				
Neutropenia	49	31	42	24
Eye				
Conjunctivitis	18	<1	3	0
Gastrointestinal				
Diarrhea	66	16	60	10
Stomatitis	31	3	19	1
Dyspepsia	16	0	9	0
General and Administration Site				
Pyrexia	26	1	14	1
Weight Decreased	15	1	9	1
Infusion Reaction[c]	14	2	<1	0
Infections				
Paronychia	20	4	<1	0
Metabolism and Nutrition				
Anorexia	30	3	23	2

Adverse Reaction	Cetuximab with FOLFIRI (n=317)		FOLFIRI Alone (n=350)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
Dermatologic				
Acne-like Rash[d]	86	18	13	<1
Rash	44	9	4	0
Dermatitis Acneiform	26	5	<1	0
Dry Skin	22	0	4	0
Acne	14	2	0	0
Pruritus	14	0	3	0
Palmar-plantar Erythrodysesthesia Syndrome	19	4	4	<1
Skin Fissures	19	2	1	0

[a] Adverse reactions occurring in ≥10% of patients in the cetuximab combination arm and at a higher incidence (≥5%) compared to the FOLFIRI alone arm.

[b] Adverse reactions were graded using the NCI CTC, version 2.0.

[c] Infusion reaction defined as any event meeting the medical concepts of allergy/anaphylaxis at any time during the clinical study or any event occurring on the first day of dosing and meeting the medical concepts of dyspnea and fever or by the following events: “acute myocardial infarction”, “angina pectoris”, “angioedema”, “autonomic seizure”, “blood pressure abnormal”, “blood pressure decreased”, “blood pressure increased”, “cardiac failure”, “cardiopulmonary failure”, “cardiovascular insufficiency”, “clonus”, “convulsion”, “coronary no-reflow phenomenon”, “epilepsy”, “hypertension”, “hypertensive crisis”, “hypertensive emergency”, “hypotension”, “infusion related reaction”, “loss of consciousness”, “myocardial infarction”, “myocardial ischemia”, “prinzmetal angina”, “shock”, “sudden death”, “syncope”, or “systolic hypertension”.

[d] Acne-like rash defined by the following events: “acne”, “acne pustular”, “butterfly rash”, “dermatitis acneiform”, “drug rash with eosinophilia and systemic symptoms”, “dry skin”, “erythema”, “exfoliative rash”, “folliculitis”, “genital rash”, “mucocutaneous rash”, “pruritus”, “rash”, “rash erythematous”, “rash follicular”, “rash generalized”, “rash macular”, “rash maculopapular”, “rash maculovesicular”, “rash morbilliform”, “rash papular”, “rash papulosquamous”, “rash pruritic”, “rash pustular”, “rash rubelliform”, “rash scarlatiniform”, “rash vesicular”, “skin exfoliation”, “skin hyperpigmentation”, “skin plaque”, “telangiectasia”, or “xerosis”.

As Single-Agent

The safety of ERBITUX with best supportive care (BSC) or BSC alone was evaluated in Study CA225-025. The data described below reflect exposure to ERBITUX in 242 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) *[see Warnings and Precautions (5.8)]*. ERBITUX was administered intravenously at the recommended dosage (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 17 infusions (range 1 to 51) *[see Clinical Studies (14.2)]*.

Table 5 provides the frequency and severity of adverse reactions in Study CA225-025.

Table 5: Selected Adverse Reactions in ≥10% of Patients with K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer Treated with Single-Agent ERBITUX (Study CA225-025)[a]

Adverse Reaction	ERBITUX with BSC (n=118)		BSC alone (n=124)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
Dermatologic				
Rash/Desquamation	95	16	21	1
Dry Skin	57	0	15	0
Pruritus	47	2	11	0
Other-Dermatology	35	0	7	2

Adverse Reaction	ERBITUX with BSC (n=118)		BSC alone (n=124)	
	Grades 1–4[b]	Grades 3 and 4	Grades 1–4	Grades 3 and 4
Nail Changes	31	0	4	0
General				
Fatigue	91	31	79	29
Fever	25	3	16	0
Infusion Reactions[c]	18	3	0	0
Rigors, Chills	16	1	3	0
Pain				
Pain-Other	59	18	37	10
Headache	38	2	11	0
Bone Pain	15	4	8	2
Pulmonary				
Dyspnea	49	16	44	13
Cough	30	2	19	2
Gastrointestinal				
Nausea	64	6	50	6
Constipation	53	3	38	3
Diarrhea	42	2	23	2
Vomiting	40	5	26	5
Stomatitis	32	1	10	0
Other	22	12	16	5
Dehydration	13	5	3	0
Mouth Dryness	12	0	6	0
Taste Disturbance	10	0	5	0
Infection				
Infection without neutropenia	38	11	19	5
Musculoskeletal				
Arthralgia	14	3	6	0
Neurological				
Neuropathy-sensory	45	1	38	2
Insomnia	27	0	13	0
Confusion	18	6	10	2
Anxiety	14	1	5	1
Depression	14	0	5	0

[a] Adverse reactions occurring in ≥10% of patients in the ERBITUX with BSC arm and at a higher incidence (≥5%) compared to the BSC alone arm.

[b] Adverse reactions were graded using the NCI CTC, version 2.0.

[c] Infusion reaction defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, sweating, tremors, shaking, drug fever, or other hypersensitivity reaction) recorded by the investigator as infusion-related.

In Combination with Irinotecan

ERBITUX at the recommended dosage was administered in combination with irinotecan in 354 patients with EGFR-expressing recurrent mCRC in Study CP02-9923 and BOND.

The most common adverse reactions were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grades 3–4 adverse reactions included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab in the studies below with the incidence of antibodies to cetuximab in other studies or to other products may be misleading.

An ELISA methodology was used to characterize the incidence of anti-cetuximab antibodies. The incidence of anti-cetuximab binding antibodies in 105 patients (from studies I4E-MC-JXBA, I4E-MC-JXBB, and I4E-MC-JXBD) with at least one post-baseline blood sample (≥4 weeks post first ERBITUX administration) was <5%.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ERBITUX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Neurologic:* Aseptic meningitis
- *Gastrointestinal:* Mucosal inflammation
- *Dermatologic:* Stevens-Johnson syndrome, toxic epidermal necrolysis, life-threatening and fatal bullous mucocutaneous disease

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, ERBITUX can cause fetal harm when administered to a pregnant woman. There are no available data for ERBITUX exposure in pregnant women. In an animal reproduction study, intravenous administration of cetuximab once weekly to pregnant cynomolgus monkeys during the period of organogenesis resulted in an increased incidence of embryolethality and abortion. Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development (*see Data*). Human IgG is known to cross the placental barrier; therefore, cetuximab may be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20% respectively.

Data

Animal Data

Pregnant cynomolgus monkeys were administered cetuximab intravenously once weekly during the period of organogenesis (gestation day [GD] 20-48) at dose levels 0.4 to 4 times the recommended dose of ERBITUX based on body surface area (BSA). Cetuximab was detected in the amniotic fluid and in the serum of embryos from treated dams on GD 49. While no fetal malformations occurred in offspring, there was an increased incidence of embryolethality and abortions at doses approximately 1 to 4 times the recommended dose of ERBITUX based on BSA.

In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development), and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ERBITUX in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG antibodies can be excreted in human milk. Due to the potential for serious adverse reactions in breastfed infants from ERBITUX, advise women not to breastfeed during treatment with ERBITUX and for 2 months after the last dose of ERBITUX.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ERBITUX *[see Use in Specific Population (8.1)]*.

Contraception

Based on its mechanism of action, ERBITUX can cause harm to the fetus when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with ERBITUX and for 2 months after the last dose of ERBITUX.

Infertility

Females

Based on animal studies, ERBITUX may impair fertility in females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ERBITUX in pediatric patients have not been established. The pharmacokinetics of cetuximab, in combination with irinotecan, were evaluated in pediatric patients with refractory solid tumors in an open-label, single-arm, dose-finding study. ERBITUX was administered once-weekly, at doses up to 250 mg/m^2, to 27 patients ranging from 1 to 12 years old; and in 19 patients ranging from 13 to 18 years old. No new safety signals were identified in pediatric patients. The pharmacokinetics of cetuximab between the two age groups were similar following a single dose of 75 mg/m^2 and 150 mg/m^2. The volume of the distribution appears to be independent of dose and approximates the vascular space of 2 L/m^2 to 3 L/m^2. Following a single dose of 250 mg/m^2, the mean $AUC_{0\text{-}inf}$ (CV%) was 17.7 mg*h/mL (34%) in the younger age group (1–12 years, n=9) and 13.4 mg*h/mL (38%) in the adolescent group (13–18 years, n=6). The mean half-life of cetuximab was 110 hours (69 to 188 hours) in the younger group and 82 hours (55 to 117 hours) in the adolescent group.

8.5 Geriatric Use

Of the 1662 patients with advanced colorectal cancer who received ERBITUX with irinotecan, with FOLFIRI or as single-agent in six studies (BOND, IMCL-CP02-9923, IMCL-CP02-0141, IMCL-CP02-0144, CA225-025 and CRYSTAL), 35% of patients were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

Clinical studies of ERBITUX conducted in patients with head and neck cancer did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Cetuximab is an epidermal growth factor receptor (EGFR) antagonist. It is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab 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. Cetuximab is produced in mammalian (murine myeloma) cell culture.

ERBITUX (cetuximab) injection for intravenous use, is a sterile, preservative-free, clear, colorless solution, which may contain a small amount of visible, white, amorphous cetuximab particulates in a single-dose vial. Each 1 mL of solution contains 2 mg of cetuximab, sodium chloride (8.48 mg), sodium phosphate dibasic heptahydrate (1.88 mg), sodium phosphate monobasic monohydrate (0.41 mg), and Water for Injection, USP at pH of 7.0 to 7.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR 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. *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab 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. Signal transduction through the EGFR results in activation of wild-type Ras proteins, but in cells with activating Ras somatic mutations, the resulting mutant Ras proteins are continuously active regardless of EGFR regulation.

In vitro, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

12.3 Pharmacokinetics

ERBITUX administered as a single-agent or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 L/h/m^2 to 0.02 L/h/m^2 as the dose increased from 20 mg/m^2 to 200 mg/m^2 and plateaued at doses >200 mg/m^2.

The systemic exposure of cetuximab after ERBITUX administration was 22% (90% CI: 6%, 38%) higher than that of another cetuximab product used in EXTREME and CRYSTAL.

Distribution

The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m^2.

Elimination

Following the recommended dosage (400 mg/m^2 initial dose; 250 mg/m^2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 μg/mL to 235 μg/mL and 41 μg/mL to 85 μg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (63 to 230 hours).

Specific Population

Age, sex, race, hepatic and renal function had no clinically significant effect on the pharmacokinetics of cetuximab. Clearance of cetuximab increased 1.8-fold as body surface area increased from 1.3 m^2 to 2.3 m^2, which is consistent with the recommended dosing of cetuximab on mg/m^2 basis.

Drug Interaction Studies

No pharmacokinetic interaction was observed between cetuximab and irinotecan, cetuximab and cisplatin, and cetuximab and carboplatin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test cetuximab for carcinogenic potential, and no mutagenic or clastogenic potential of cetuximab was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. Menstrual cyclicity was impaired in female cynomolgus monkeys receiving weekly doses of 0.4 to 4 times the recommended dose of ERBITUX (based on total body surface area). Cetuximab-treated animals exhibited increased incidences of irregular or absent cycles, as compared to control animals. These effects were initially noted beginning on week 25 and continued through the 6-week recovery period. No effects of cetuximab were observed on measured male fertility parameters (i.e., serum testosterone levels and analysis of sperm counts, viability, and motility) as compared to control male monkeys.

14 CLINICAL STUDIES

14.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

In Combination with Radiation Therapy

BONNER (NCT00004227) was a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced SCCHN. Patients with Stage III/IV SCCHN of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive either ERBITUX in combination with radiation therapy or radiation therapy alone. Stratification factors were Karnofsky performance status (60–80 versus 90–100), nodal stage (N0 versus N+), tumor stage (T1–3 versus T4 using American Joint Committee on Cancer 1998 staging criteria), and radiation therapy fractionation (concomitant boost versus once-daily versus twice-daily). Radiation therapy was administered for 6–7 weeks as once-daily, twice-daily, or concomitant boost. ERBITUX was administered intravenously as a 400 mg/m^2 initial dose beginning one week prior to initiation of radiation therapy, followed by 250 mg/m^2 weekly administered 1 hour prior to radiation therapy for the duration of radiation therapy (6–7 weeks). The main efficacy outcome measure was duration of locoregional control. Another outcome measure was overall survival (OS).

Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were White, and 90% had baseline Karnofsky performance status ≥80. There were 258 patients enrolled in U.S. sites (61%). Sixty percent of patients had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

Efficacy results are presented in Table 6.

Table 6: Efficacy Results in Locoregionally Advanced SCCHN in BONNER

	ERBITUX plus Radiation (n=211)	Radiation Alone (n=213)	Hazard Ratio (95% CI[a])	Stratified Log-rank p-value
Locoregional Control				
Median duration (months)	24.4	14.9	0.68 (0.52–0.89)	0.005
Overall Survival				
Median duration (months)	49.0	29.3	0.74 (0.57–0.97)	0.03

[a] CI = confidence interval.

In Combination with Platinum-based Therapy with Fluorouracil

EXTREME (NCT00122460) was an open-label, randomized, multicenter, controlled trial of 442 patients with recurrent locoregional disease or metastatic SCCHN. Patients with no prior therapy for recurrent locoregional disease or metastatic SCCHN were randomized (1:1) to receive a cetuximab product in combination with platinum-based therapy and fluorouracil or platinum-based therapy and fluorouracil alone. Choice of cisplatin or carboplatin was at the discretion of the investigator. Stratification factors were Karnofsky performance status (<80 versus ≥80) and previous chemotherapy. Cisplatin (100 mg/m^2 intravenously on Day 1) or carboplatin (AUC 5 mg/mL*min intravenously on Day 1) and fluorouracil (1000 mg/m^2/day intravenously on Days 1–4) were administered every 3 weeks (1 cycle) for a maximum of 6 cycles in the absence of disease progression or unacceptable toxicity. Cetuximab was administered intravenously at a 400 mg/m^2 initial dose, followed by a 250 mg/m^2 weekly dose. In the absence of disease progression or unacceptable toxicity after completion of 6 planned courses of platinum-based therapy, weekly cetuximab as a single-agent could be continued until disease progression or unacceptable toxicity. If chemotherapy was delayed because of adverse reactions, weekly cetuximab was continued. If chemotherapy was discontinued for adverse reactions, weekly cetuximab as a single-agent could be continued until disease progression or unacceptable toxicity. The main efficacy outcome measure was OS. Other outcome measures were PFS and objective response rate (ORR).

Of the 442 randomized patients, the median age was 57 years, 90% were male, 98% were White, and 88% had baseline Karnofsky performance status ≥80. Thirty-four percent of patients had oropharyngeal, 25% laryngeal, 20% oral cavity, and 14% hypopharyngeal primary tumors. Fifty-three percent of patients had recurrent locoregional disease only and 47% had metastatic disease. Fifty-eight percent had AJCC Stage IV disease and 21% had Stage III disease. Sixty-four percent of patients received cisplatin therapy and 34% received carboplatin as initial therapy. Approximately fifteen percent of the patients in the cisplatin alone arm switched to carboplatin during the treatment period.

Efficacy results are presented in Table 7 and Figure 1.

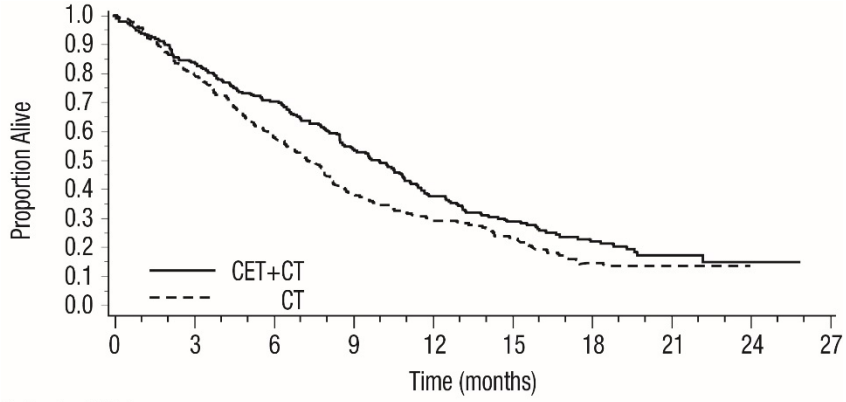
Table 7: Efficacy Results in Recurrent Locoregional Disease or Metastatic SCCHN in EXTREME

	Cetuximab with Platinum-based Therapy and Fluorouracil (n=222)	Platinum-based Therapy and Fluorouracil (n=220)
Overall Survival		
Median Duration (months)	10.1	7.4
Hazard Ratio (95% CI[a])	0.80 (0.64, 0.98)	
Stratified Log-rank p-value	0.034	
Progression-free Survival		
Median Duration (months)	5.5	3.3
Hazard Ratio (95% CI[a])	0.57 (0.46, 0.72)	
Stratified Log-rank p-value	<0.0001	
Objective Response Rate	35.6%	19.5%
Odds Ratio (95% CI[a])	2.33 (1.50, 3.60)	
CMH[b] Test p-value	0.0001	

[a] CI = confidence interval.

[b] CMH = Cochran-Mantel-Haenszel.

Figure 1: Kaplan-Meier Curves for Overall Survival in Patients with Recurrent Locoregional Disease or Metastatic SCCHN in EXTREME



CT = Platinum-based therapy with fluorouracil

CET = another cetuximab product

In exploratory subgroup analyses by initial platinum therapy (cisplatin or carboplatin), for patients (N=284) receiving cetuximab in combination with cisplatin and fluorouracil compared to cisplatin and fluorouracil alone, the difference in median OS was 3.3 months (10.6 versus 7.3 months; HR 0.71; 95% CI 0.54, 0.93). The difference in median PFS was 2.1 months (5.6 versus 3.5 months; HR 0.55; 95% CI 0.41, 0.73). The ORR was 39% and 23%, respectively (OR 2.18; 95% CI 1.29, 3.69).

For patients (N=149) receiving cetuximab in combination with carboplatin and fluorouracil compared to carboplatin and fluorouracil alone, the difference in median OS was 1.4 months (9.7 versus 8.3 months; HR 0.99; 95% CI 0.69, 1.43). The difference in median PFS was 1.7 months (4.8 versus 3.1 months, respectively; HR 0.61; 95% CI 0.42, 0.89). The ORR was 30% and 15%, respectively (OR 2.45; 95% CI 1.10, 5.46).

As Single-Agent
EMR 62202-016 was a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN. All patients had documented disease progression within 30 days of a platinum-based chemotherapy regimen. Patients were administered intravenously 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.

The median age was 57 years, 82% were male, 100% White, and 62% had a Karnofsky performance status of ≥80.

The ORR was 13% (95% CI 7%, 21%). Median duration of response (DoR) was 5.8 months (range 1.2 to 5.8 months).

14.2 K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer (CRC)

In Combination with FOLFIRI

CRYSTAL (NCT00154102) was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, mCRC. Patients were randomized (1:1) to receive either a cetuximab product in combination with FOLFIRI or FOLFIRI alone as first-line treatment. Stratification factors were Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 versus 2) and region (Western Europe versus Eastern Europe versus other).

FOLFIRI regimen included 14-day cycles of irinotecan (180 mg/m^2 intravenously on Day 1), folinic acid (400 mg/m^2 [racemic] or 200 mg/m^2 [L-form] intravenously on Day 1), and fluorouracil (400 mg/m^2 bolus on Day 1 followed by 2400 mg/m^2 as a 46-hour continuous infusion). Cetuximab was administered intravenously as a 400 mg/m^2 initial dose , followed by 250 mg/m^2 weekly administered 1 hour prior to chemotherapy. Study treatment continued until disease progression or unacceptable toxicity. The main efficacy outcome measure was PFS assessed by an independent review committee (IRC). Other outcome measures were OS and ORR.

Of the 1217 randomized patients, the median age was 61 years, 60% were male, 86% were White, and 96% had a baseline ECOG performance status 0–1, 60% had primary tumor localized in colon, 84% had 1–2 metastatic sites and 20% had received prior adjuvant and/or neoadjuvant chemotherapy. Demographics and baseline characteristics were similar between study arms.

K-Ras mutation status was available for 89% of the patients: 63% had K-Ras wild-type tumors and 37% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D. Baseline characteristics and demographics in the K-Ras wild-type subset were similar to that seen in the overall population.

A statistically significant improvement in PFS was observed for the cetuximab with FOLFIRI arm compared with the FOLFIRI arm (median PFS 8.9 vs. 8.1 months, HR 0.85 [95% CI 0.74, 0.99], p-value=0.036). OS was not significantly different at the planned, final analysis based on 838 events (HR=0.93, 95% CI [0.8, 1.1], p-value 0.327).

Results of the planned PFS and ORR analysis in all randomized patients and post-hoc PFS and ORR analysis in subgroups of patients defined by K-Ras mutation status, and post-hoc analysis of updated OS based on additional follow-up (1000 events) in all randomized patients and in subgroups of patients defined by K-Ras mutation status are presented in Table 8 and Figure 2. The treatment effect in the all-randomized population for PFS was driven by treatment effects limited to patients who have K-Ras wild-type tumors. There is no evidence of effectiveness in the subgroup of patients with K-Ras mutant tumors.

Table 8: Efficacy Results in First-line EGFR-expressing, Metastatic Colorectal Cancer in CRYSTAL (All Randomized and K-Ras Status)

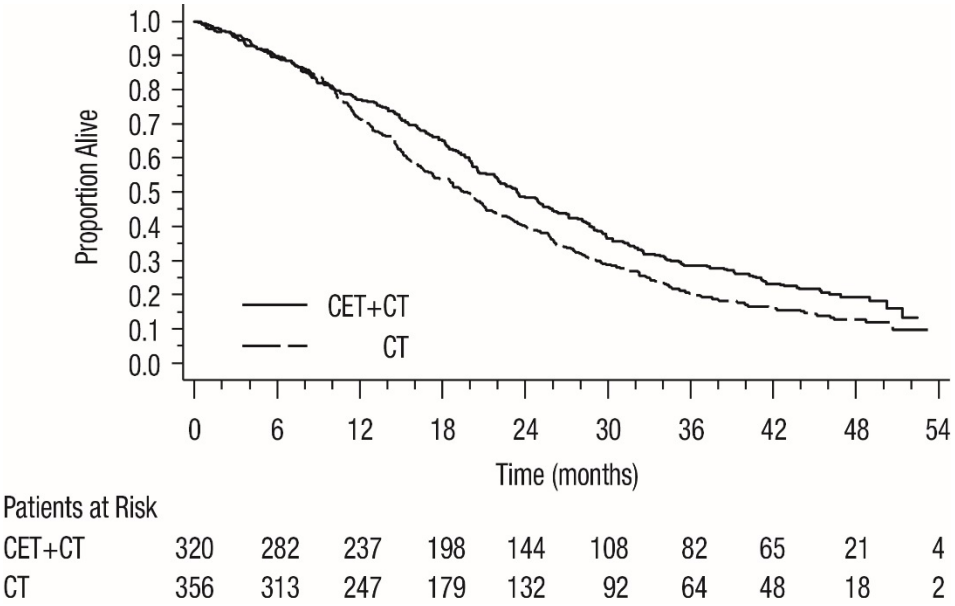
	All Randomized		**K-Ras Wild-type**		**K-Ras Mutant**	
	Cetuximab with FOLFIRI (n=608)	**FOLFIRI (n=609)**	**Cetuximab with FOLFIRI (n=320)**	**FOLFIRI (n=356)**	**Cetuximab with FOLFIRI (n=216)**	**FOLFIRI (n=187)**
Progression-Free Survival						
Number of Events (%)	343 (56)	371 (61)	165 (52)	214 (60)	138 (64)	112 (60)
Median (months) (95% CI)	8.9 (8.0, 9.4)	8.1 (7.6, 8.8)	9.5 (8.9, 11.1)	8.1 (7.4, 9.2)	7.5 (6.7, 8.7)	8.2 (7.4, 9.2)
HR (95% CI)	0.85 (0.74, 0.99)		0.70 (0.57, 0.86)		1.13 (0.88, 1.46)	

	All Randomized		K-Ras Wild-type		K-Ras Mutant	
	Cetuximab with FOLFIRI (n=608)	**FOLFIRI (n=609)**	**Cetuximab with FOLFIRI (n=320)**	**FOLFIRI (n=356)**	**Cetuximab with FOLFIRI (n=216)**	**FOLFIRI (n=187)**
p-value[a]	0.0358					
Overall Survival[b]						
Number of Events (%)	491 (81)	509 (84)	244 (76)	292 (82)	189 (88)	159 (85)
Median (months) (95% CI)	19.6 (18, 21)	18.5 (17, 20)	23.5 (21, 26)	19.5 (17, 21)	16.0 (15, 18)	16.7 (15, 19)
HR (95% CI)	0.88 (0.78, 1.0)		0.80 (0.67, 0.94)		1.04 (0.84, 1.29)	
Objective Response Rate						
ORR (95% CI)	46% (42, 50)	38% (34, 42)	57% (51, 62)	39% (34, 44)	31% (25, 38)	35% (28, 43)

[a] Based on the Stratified Log-rank test.

[b] Post-hoc updated OS analysis, results based on an additional 162 events.

Figure 2: Kaplan-Meier Curves for Overall Survival in the K-Ras Wild-type Population in CRYSTAL



As Single-Agent

Study CA225-025 (NCT00079066) was a multicenter, open-label, randomized, clinical trial conducted in 572 patients with EGFR-expressing, previously treated, recurrent mCRC. Patients were randomized (1:1) to receive either ERBITUX with best supportive care (BSC) or BSC alone. ERBITUX was administered intravenously as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. The main efficacy outcome measure was OS. Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were White, and 77% had baseline ECOG performance status of 0–1. Demographics and baseline characteristics were similar between study arms. All patients were to have received and progressed on prior therapy including an irinotecan-containing regimen and an oxaliplatin-containing regimen.

K-Ras status was available for 79% of the patients: 54% had K-Ras wild-type tumors and 46% had K-Ras mutant tumors where testing assessed for the following somatic mutations in codons 12 and 13 (exon 2): G12A, G12D, G12R, G12C, G12S, G12V, G13D.

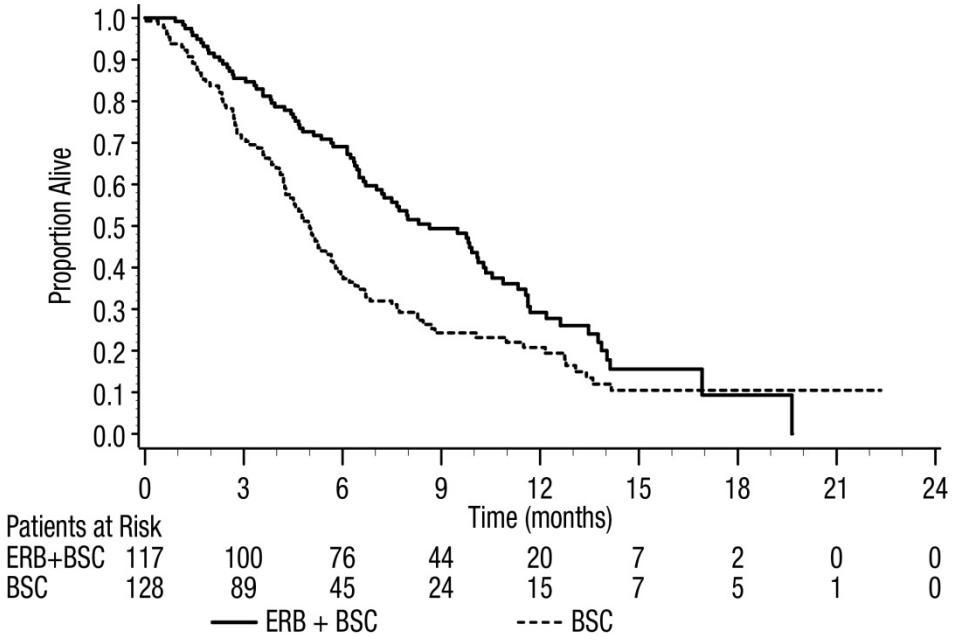
Efficacy results are presented in Table 9 and Figure 3.

Table 9: Overall Survival in Previously Treated EGFR-expressing, Metastatic Colorectal Cancer in Study CA225-025 (All Randomized and K-Ras Status)

	All Randomized		K-Ras Wild-type		K-Ras Mutant	
	ERBITUX with BSC (N=287)	BSC (N=285)	ERBITUX with BSC (N=117)	BSC (N=128)	ERBITUX with BSC (N=108)	BSC (N=100)
Median (months) (95% CI)	6.1 (5.4, 6.7)	4.6 (4.2, 4.9)	8.6 (7.0, 10.3)	5.0 (4.3, 5.7)	4.8 (3.9, 5.6)	4.6 (3.6, 4.9)
HR (95% CI)	0.77 (0.64, 0.92)		0.63 (0.47, 0.84)		0.91 (0.67, 1.24)	
p-value[a]	0.0046					

[a] Based on the Stratified Log-rank test.

Figure 3: Kaplan-Meier Curves for Overall Survival in Patients with K-Ras Wild-type Metastatic Colorectal Cancer in Study CA225-025



In Combination with Irinotecan

BOND was a multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent mCRC. Tumor specimens were not available for testing for K-Ras mutation status. Patients were randomized (2:1) to receive either ERBITUX in combination with irinotecan (218 patients) or ERBITUX single-agent (111 patients). ERBITUX was administered intravenously as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. In the ERBITUX with irinotecan arm, irinotecan was added to ERBITUX using the same dosage 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. The efficacy of ERBITUX with irinotecan or ERBITUX single-agent, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures.

Of the 329 patients, the median age was 59 years, 63% were male, 98% were White, and 88% had baseline Karnofsky performance status ≥80. Approximately two-thirds had previously failed oxaliplatin treatment.

In patients receiving ERBITUX with irinotecan, the ORR was 23% (95% CI 18%, 29%), median DoR was 5.7 months, and median time to progression was 4.1 months. In patients receiving ERBITUX as a single-agent, the ORR was 11% (95% CI 6%, 18%), median DoR was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and single-agent arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ERBITUX® (cetuximab) injection is a sterile, preservative-free, clear, colorless solution in a 2 mg/mL single-dose vial supplied as follows:

- 100 mg/50 mL individually packaged in a carton (NDC 66733-948-23)
- 200 mg/100 mL individually packaged in a carton (NDC 66733-958-23)

Storage and Handling

- Store vials under refrigeration at 2° C to 8° C (36° F to 46° F).
- Do not freeze or shake.
- Increased particulate formation may occur at temperatures at or below 0° C (32° F).
- Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C.
- Discard any unused portion of the vial.

17 PATIENT COUNSELING INFORMATION

Infusion Reactions

Advise patients that the risk of serious infusion reactions may be increased in patients who have had a tick bite or red meat allergy. Advise patients to contact their healthcare provider and to report signs and symptoms of infusion reactions, including late onset infusion reactions, such as fever, chills, or breathing problems *[see Warnings and Precautions (5.1)]*.

Cardiopulmonary Arrest

Advise patients of the risk of cardiopulmonary arrest or sudden death and to report any history of coronary artery disease, congestive heart failure, or arrhythmias *[see Warnings and Precautions (5.2)]*.

Pulmonary Toxicity

Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.3)]*.

Dermatologic Toxicities

Advise patients to limit sun exposure during ERBITUX treatment and for 2 months after the last dose of ERBITUX. Advise patients to notify their healthcare provider of any sign of acne-like rash, (which can include itchy, dry, scaly, or cracking skin and inflammation, infection or swelling at the base of the nails or loss of the nails), conjunctivitis, blepharitis, or decreased vision *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

Advise female patients of reproductive potential of the potential risk to a fetus and to use effective contraception during ERBITUX treatment and for 2 months after the last dose of ERBITUX. Advise patients to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8), Use in Specific Populations (8.3)]*.

Lactation

Advise patients not to breastfeed during ERBITUX treatment and for 2 months after the last dose of ERBITUX *[see Use in Specific Populations (8.2)]*.

Manufactured by ImClone LLC a wholly-owned subsidiary of Eli Lilly and Company, Branchburg, NJ 08876 USA

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License No. 1827

ERB-0008-USPI-202104

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA B DONOGHUE
04/06/2021 02:08:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084Orig1s277, s280

CLINICAL REVIEW(S)

Clinical and Statistical Review of Supplemental Biologics License Application

Application type	Supplemental Biologics License Application (SE2 Efficacy Supplement)
Application number	sBLA 125084 (Supplements 277 and 280)
Priority or Standard	Standard
Submission date	November 19, 2020
Approval date	April 6, 2021
Division/Office	Division of Oncology 2 (DO2)/Office of Oncologic Diseases (OOD)
Reviewer/Team Leader	Clinical: Janice Kim, PharmD/Nicole Drezner, MD Statistics: Xiaoxue Li, PhD/Pallavi Mishra-Kalyani, PhD
Established name	Cetuximab
Trade name	Erbitux
Therapeutic class	Monoclonal antibody against EGFR
Applicant	Eli Lilly
Proposed labeling change	Addition of biweekly (every 2 weeks [Q2W]) dosage regimen as a single agent or in combination with chemotherapy for the treatment of patients with: • K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) or • recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck (SCCHN). New dosage regimen: 500 mg/m^2 Q2W administered as 120-minute intravenous infusions
Recommendation	Regular Approval

Regulatory background

Cetuximab, a monoclonal antibody that inhibits epidermal growth factor receptor (EGFR), was initially approved in 2004 for the treatment of EGFR-expressing colorectal cancer (CRC). Cetuximab is currently approved for the treatment of:

- Squamous Cell Carcinoma of the Head and Neck (SCCHN):
  - In combination with radiation therapy for the initial treatment of locally or regionally advanced SCCHN
  - In combination with platinum-based therapy with fluorouracil for the first-line treatment of patients with recurrent locoregional disease or metastatic SCCHN
  - As a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed

- K-RAS wild-type, EGFR-expressing, metastatic colorectal cancer (mCRC) as determined by an FDA-approved test:
    - In combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) for first-line treatment
    - In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy
    - As a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan

  Limitation of Use: cetuximab is not indicated for the treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

Prior to approval of this sBLA, when used as a single-agent or in combination with platinum-based therapy and fluorouracil (for SCCHN) or as a single agent or in combination with irinotecan or FOLFIRI (for mCRC), the approved dosage regimen was 400 mg/m^2 as an initial loading dose administered as a 120-minute IV infusion followed by a weekly (Q1W) maintenance dose of 250 mg/m^2 infused over 60 minutes.

Eli Lilly submitted this sBLA to add a biweekly (Q2W) dosage regimen for cetuximab for use in mCRC and recurrent/metastatic SCCHN. The proposed dosing schedule is 500 mg/m^2 administered every 2 weeks. A model-informed drug development (MIDD) approach was used to inform the dosage change (Table 1). To provide supportive clinical evidence for the addition of the Q2W dosage regimen, Eli Lilly performed a meta-analysis of published clinical data as well as a real-world evidence (RWE) analysis. Both the literature review and RWE data analysis compared the efficacy and safety outcomes of the Q1W and Q2W regimens.

Table 1: Key Regulatory Interactions

Date	Description
March 11, 2020	Lilly submitted request to FDA for Model-Informed Drug Development (MIDD) (IND 005804) meetings to discuss using a MIDD approach to support the approval of a Q2W dosing schedule for cetuximab for the approved indications for recurrent or metastatic disease.
June 25, 2020	Initial MIDD meeting between Lilly and FDA. FDA provided feedback on Lilly's proposed approach for demonstrating comparability between the two dosing schedules and requested that the following additional information be included in the subsequent MIDD meeting: • Information pertaining to target occupancy and dose/exposure-response for efficacy to assess the clinical

Date	Description
	relevance of the lower steady-state trough concentrations following the proposed 500 mg/m^2 Q2W dosing compared to that with the current approved 250 mg/m^2 Q1W dosing. Please also provide information on doses higher than 500 mg/m^2 [e.g., from the original dose escalation/selection trial] to support safety. • A tabular description of each trial included in the literature analysis including the inclusion/exclusion criteria of the studies, geographical location of the trials, baseline characteristics of the patients, and the exact timing of the different trials. • Any available clinical safety and efficacy data from company sponsored clinical trials (and any other clinical trials for which Eli Lilly has rights and access to the data [e.g., CRYSTAL]) to support the safety of cetuximab 500 mg/m^2 Q2W. • Any available clinical data from the cetuximab clinical development program for patients with SCCHN and CRC receiving cetuximab 500 mg/m^2 Q2W • Recommendation to conduct a comprehensive literature search for clinical studies using cetuximab 500 mg/m^2 Q2W in patients with SCCHN and provide information for which Lily has right of reference and access.
August 26, 2020	Agreement on a sufficient data package to evaluate the addition of a cetuximab Q2W dosage regimen for the mCRC and SCCHN indications was reached. FDA agreed that the available clinical and model-predicted PK data along with supplemental clinical data from literature and RWE are sufficient to evaluate the addition of the cetuximab Q2W dosing schedule for the mCRC and SCCHN indications. FDA reiterated that the demonstration of PK comparability is the primary evidence of interest and that the supplemental clinical data from the literature and RWE are considered supportive.

Source: Clinical Overview submission

Analyses from Published Literature

Eli Lilly performed a systematic literature review on PubMed and RightFind for publications issued from 2007 through the date of supplement submission (November 19, 2020) for clinical

studies of cetuximab administered either using a Q1W or Q2W schedule in patients with K-RAS wild-type mCRC and SCCHN.

mCRC

Studies in which cetuximab was administered to patients with mCRC were selected for analysis if the following study criteria were met:

- Patients received cetuximab Q2W at the proposed 500 mg/m^2 dose;
- Included adult patients diagnosed with wild-type K-RAS mCRC;
- Reported efficacy outcomes or adverse events (AEs); and
- Had a randomized/non-randomized or single arm design.

Eight studies were identified and of these, two were excluded due to the limited number of patients enrolled at the Q2W dose level and substantially different patient characteristics compared to the rest of the studies. Table 2 provides a summary of the study design, sample size, treatment information and decision regarding inclusion of the study in the analysis. The efficacy results aggregated from the 6 studies included were compared with those observed in the CRYSTAL study, which supported the approval of cetuximab in combination with FOLFIRI for the treatment of patients with mCRC. CRYSTAL was an open-label, randomized trial of cetuximab in combination with 5-FU and irinotecan (FOLFIRI) versus FOLFIRI. Patients randomized to the cetuximab arm received the Q1W cetuximab dosage regimen, consisting of 400 mg/m^2 for the first infusion then weekly intravenous infusions of 250 mg/m^2.

Table 2: Summary of studies evaluating the proposed Q2W cetuximab dosage regimen

Trial Alias	Author, Year	Treatment	Trial Design	N	Selection decision for meta-analysis
CECOG	Brodowicz et al., 2013	CET (Q1W) + FOLFOX vs CET (Q2W) + FOLFOX	Phase 2, Randomized	Q2W = 77	Included
OPTIMAX-ACROSS	Fernandez-Planaet et al., 2014	CET + FOLFOX-4	Phase 2, Single Arm	Q2W = 99	Included
APEC	Cheng et al., 2017	CET + FOLFIRI	Phase 2, Single Arm	Q2W = 101	Included
APEC	Cheng et al., 2017	CET + FOLFOX	Phase 2, Single Arm	Q2W = 188	Included
CELINE	Kotake et al., 2017	CET + 5-FU + FOLFOX6	Phase 2, Single Arm	Q2W = 60	Included
NORDIC 7.5	Pfeiffer et al., 2015	FLOX + CET for 16 weeks then maintenance CET (Q1W vs Q2W)	Phase 2, Single Arm,	Q2W = 152	Included
EMR62202-045	Tabernero et al.,	CET followed by CET + FOLFIRI	Phase 1, PK/PD	62 receiving	Not included due to limited sample size;

Trial Alias	Author, Year	Treatment	Trial Design	N	Selection decision for meta-analysis
	2010a			various dose level	14 patients received 500 mg/m^2 Q2W
FLEET2	Hazama et al., 2016	CET + XELOX	Phase 2, Single Arm	Q2W = 26	Not included due to small sample size with substantially different patient characteristics

Source: Clinical Overview submission

Abbreviations: CET – Cetuximab; FLOX – 5-FU, folinic acid, oxaliplatin; FOLFOX – folinic acid, 5-FU, oxliplatin; XELOX – capecitabine, oxliplatin; FOLFIRI – folinic acid, 5-FU, irinotecan

The inclusion/exclusion criteria were similar between studies and the baseline characteristics of patients enrolled in the studies included in the analysis were generally comparable (Table 3). In one study (APEC), cetuximab Q2W was administered in combination with FOLFIRI.

Table 3: Baseline Characteristics of Patients Enrolled in mCRC Studies Identified in the systematic Literature Review

Study	CECOG	APEC (FOLFOX)	APEC (FOLFIRI)	OPTIMIX-ACROSS	CELINE	NORDIC-7.5	CRYSTAL
N of patients with K-Ras wild-type mCRC	77	188	101	99	60	152	316
Age in years median, range	62 (30-75)	NR	NR	64 (34-82)	64 (38-82)	64 (NR)	61 (24-79)
Ethnicity (%): Asian Caucasian Other	NR	89 11 0	91 8 1	NR 99 1	NR	NR	NR 87 NR
ECOG PS, % 0 1 2	42 58 0	NR	NR	52 49 0	85 15 0	67 26 6	58 38 4
Primary tumor location (%) Colon Rectum	71 29	56 38	51 45	60 40	50 50	57 NR	58 40
Liver metastases only (%)	30	29	30	NR	NR	13	22
Patients with >2 organ metastasis (%)	29	NR	NR	NR	20	NR	10
Prior Adjuvant (%)	NR	21	47	9	7	7	25

NR: not reported
Source: Clinical Overview in sBLA submission

mCRC – Efficacy results

The efficacy results for the analysis of mCRC studies are provided in Table 4. A fixed effect model and random-effect models were used to aggregate data from the studies. No patient-level data from the studies were available, so trial level estimates of ORR, landmark PFS rates, and landmark OS rates observed in the studies were used. The results of the analysis of each endpoint were numerically similar to the results from the CRYSTAL study, with overlapping confidence intervals, suggesting that the observed efficacy results in patients receiving cetuximab at the Q1W or Q2W schedule are comparable.

Table 4: Efficacy Results for mCRC Analysis

Trial	N	ORR, % 95% CI	PFS Rate, % (95% CI)			OS Rate, % (95% CI)			
			6 Mo	12 Mo	18 Mo	6 Mo	12 Mo	24 Mo	36 Mo
CECOG	Q2W = 77	62 (51,73)	75 (65, 84)	33 (23, 44)	18 (11, 28)	91 (82, 96)	77 (66, 85)	47 (36, 58)	25 (16, 35)
OPTIMAX-ACROSS	Q2W = 99	61 (50,70)	82 (73, 88)	62 (49, 73)	14 (9, 23)	93 (86, 97)	78 (69, 85)	49 (40, 59)	24 (17,34)
APEC	Q2W = 101	55 (44,64)	73 (64, 81)	33 (25, 43)	28 (20, 37)	92 (85, 96)	83 (75, 89)	57 (48, 67)	37 (28, 46)
APEC	Q2W = 188	61 (54,68)	76 (69, 82)	45 (35, 54)	26 (20, 33)	89 (84, 93)	81 (75, 86)	54 (47, 61)	31 (25, 38)
CELINE	Q2W = 60	70 (57, 81)	82 (70, 90)	32 (25, 40)	37 (26, 50)	90 (80, 95)	78 (66, 87)	58 (46, 70)	NA*
NORDIC-7.5	Q2W = 152	62 (54, 69)	74 (67, 81)	33 (23, 44)	14 (9, 20)	90 (84, 94)	76 (69, 82)	48 (40, 56)	28 (22, 36)
Pooled Q2W	Q2W = 677	61 (57, 65)	76 (73, 79)	40 (36, 44)	23 (20, 26)	91 (88, 93)	79 (76, 82)	52 (48, 56)	30 (26, 33)
CRYSTAL	Q1W = 316	57 (52, 63)	73 (67, 78)	39 (32, 47)	23 (20, 26)	90 (86, 92)	78 (73, 82)	49 (43, 54)	29 (24, 34)

* No data available in CELINE for 36 months OS rate

Source: summarized from BLA 125084 s277, Clinical Study Report

The analysis conducted by Eli Lilly included studies with different types of backbone chemotherapy combinations, including FOLFIRI (one study) and regimens including platinum-5FU-based chemotherapy (five studies); patients received FOLFIRI as backbone therapy in the CRYSTAL study. To explore this issue further, the FDA requested that Eli Lilly provide a subset analysis comparing the overall response rate (ORR) observed in the cetuximab arm of the CRYSTAL study to the ORR observed in the subset of patients who received the same chemotherapy regimen in combination with cetuximab Q2W in the APEC trial (101 of the 188 patients randomized to the Q2W regimen). In this analysis, the ORR in patients who received FOLFIRI and the Q1W cetuximab dosage regimen in the CRYSTAL trial was comparable to the

ORR in patients who received FOLFIRI and the cetuximab Q2W dosage regimen in APEC (Table 5).

Table 5: Overall Response Rate in Patients Receiving Cetuximab and FOLIRI

Study	(K-Ras Wild-type)	ORR (%, 95%CI)
APEC – FOLFIRI (Q2W)	101	55 (44-64)
CRYSTAL – FOLFIRI (Q1W)	316	57 (52-63)

Source: Eli Lilly IR Response Document, February 19, 2021

mCRC - Safety

The meta-analysis safety outcomes included the incidence of clinically relevant Grade 3-4 AEs including paronychia, neutropenia, diarrhea, acne-like rash, rash, dermatitis acneiform, palmar-plantar erythyodysesthesia syndrome, cardiopulmonary arrest, IRR, hypomagnesemia, nail toxicity and sepsis. A comparison of the incidence of Grade 3-4 adverse events observed in patients who received the Q2W and Q1W dosage regimens is provided in Table 6. There was no substantial difference in the incidence of most of these select adverse events between the two dosing regimens; however, events of cardiopulmonary arrest, hypomagnesemia, and sepsis occurred in patients receiving Q2W dosing and were not reported in the CRYSTAL study. Since the Warnings and Precautions section of cetuximab product labeling, which describes adverse reactions observed in patients who received the Q1W cetuximab dosage regimen, describes the risk of cardiopulmonary arrest and hypomagnesemia with cetuximab, these adverse reactions are likely not due to the Q2W dosage regimen. Sepsis is not uncommon in patients with advanced cancer who are receiving chemotherapy and is not likely attributable to changes in the cetuximab dosing schedule

Table 6: Incidence Rate of Grade 3-4 Adverse Events in Published Literature vs. CRYSTAL Study

Rate of Grade 3-4 AEs (%)	Q2W pooled N=677 Rate, %, (95% CI)	APEC-FOLFIRI (Q2W) N=101 Rate, %, (95% CI)	CRYSTAL (Q1W) N=317 Rate, %, (95% CI)
Paronychia	11 (8-14)	10 (5-17)	4 (NR)
Neutropenia	37 (34-41)	36 (27-45)	31 (26-36)
Diarrhea	10 (8-13)	11 (7-20)	16 (13-21)
Rash	12 (10-15)	4 (2-10)	9 (6-13)
Dermatitis Acneiform	5 (3-8)	5 (2-11)	5 (3-8)
Palmar-plantar Erythrodysesthesia syndrome	4 (2-7)	2 (1-8)	4 (NR)
Cardiopulmonary arrest	2 (1-5)	3 (1-9)	NR
Hypomagnesemia	1 (0.3-5)	NR	NR
Sepsis	3 (2-6)	4 (2-10)	NR
Acne-like rash	18 (14-22)	11 (6-19)	16 (13-21)

Rate of Grade 3-4 AEs (%)	Q2W pooled N=677 Rate, %, (95% CI)	APEC-FOLFIRI (Q2W) N=101 Rate, %, (95% CI)	CRYSTAL (Q1W) N=317 Rate, %, (95% CI)
Infusion-related reaction	3 (2-6)	0	2 (1-4)

NR: not reported
Source: Clinical Overview submission, Erbitux USPI

SCCHN

Six studies were identified that met the following inclusion criteria for the SCCHN meta-analysis:

- Enrolled patients with locoregionally recurrent and/or metastatic SCCHN who were treated with cetuximab in combination with platinum-based therapy or cetuximab monotherapy;
- Study reported outcome of efficacy (PFS, OS, ORR) or incidence of AEs; and
- Randomized/non-randomized or single-arm trials and prospective studies.

Three different trials supported the approvals of cetuximab for the SCCHN indications, including the BONNER, EXTREME, and EMR 62202-016 studies. The studies included in the meta-analysis were generally comparable to each other with respect to eligibility criteria and patient baseline characteristics (Table 8); however, the studies included from published literature included patients with SCCHN who received cetuximab Q2W and who had received zero to various lines of prior therapy. Furthermore, the literature search did not identify studies in the US in which patients received cetuximab Q2W for treatment of the approved SCCHN indications. Therefore, a limitation of the SCCHN analysis is the use of a heterogeneous population of patients across the included studies, specifically regarding number of prior lines of therapy received and therapies received in combination with cetuximab. Because the efficacy results for the group of patients who received cetuximab Q2W are not comparable to the results from the BONNER, EXTREME, and EMR 62202-016 studies (in which patients received cetuximab Q1W), the analysis supporting the comparability of the Q1W and Q2W dosage regimens in SCCHN focuses on a comparison of the results of the trials included in the literature search rather than a comparison of the results of the literature search trials to the results of the BONNER, EXTREME, and EMR-62202-016 studies. The studies included in the literature analysis are described in Table 7.

Table 7: Summary of Studies Contributing to Safety and Efficacy Evaluations

Study	Treatment	Trial Design	Prior Therapy	N (Randomized to Cetuximab)
Fury et al. (2012)	CET Q2W (500) vs CET Q2W (750)	Ph 2, Randomized	Received 0-2 prior cytotoxic chemotherapy regimens for recurrent/metastatic disease	35
Kochanny et al. (2020)	Tivantinib + CET Q2W (500) vs CET Q2W (500)	Ph 2, Randomized	Received 0-2 prior palliative cytotoxic treatments	38
Ruzsa et al. (2014)	EMD 1201081 + CET Q1W (250) vs CET Q1W (250)	Ph 2, Randomized	Received 0-1 prior palliative chemotherapy regimen for recurrent, refractory or metastatic disease	53
Jimeno et al. (2015)	PX-866 + CET Q1W (250) vs CET Q1W (250)	Ph 2, Randomized	Received 1-2 prior systemic therapies, including up to one platinum-based chemotherapy regimen	41
Gilbert et al. (2015)	Sorafenib + CET Q1W (250) vs CET Q1W (250)	Ph 2, Randomized	Progressing on a first-line cytotoxic chemotherapy regimen	27
Fayette et al. (2016)	Duligotuzumab vs CET Q1W (250)	Ph 2, Randomized	Progressed after one or more lines of treatment, at least one platinum-based regimen for recurrent/metastatic disease, and not suitable for local therapy	62

Source: Clinical Overview submission
Abbreviations: CET - cetuximab; Ph 2 – Phase 2; Q1W – weekly; Q2W – biweekly

Table 8: Baseline Characteristics of Patients for SCCHN Studies Identified in Systematic Literature Review

Study	Fury et al. 2012	Kochanny et al. 2020	Gilbert et al. 2015	Jimeno et al. 2014	Ruzsa et al. 2014	Fayette et al. 2016
N for Cetuximab randomized	35	38	27	41	53	62
Age in years Median (range)	59 (46-84)	63.6 (35-87)	59 (NR)	63 (39-83)	57 (NR)	62 (28-84)
Male (%)	80	85	93	93	85	75
Any prior systemic therapy (%)	63	87	50	51	100	>50
Caucasian (%)	NR	84	89	75	100	74
ECOG PS or Equivalent (%) 0 1 2	 31 51 17	 50 50 -	 11 52 33	 20 80 -	 23 77 -	 85
Prior radiotherapy (%)	94	NR	NR	24	77	84

SCCHN - Efficacy

The endpoints for this analysis included ORR, landmark PFS rates at 3 months and 6 months, and landmark OS rates at 6 and 12 months (Table 9). The results for all endpoints were numerically similar and the 95% confidence intervals overlapped across all studies, as well as for the pooled analysis.

Table 9: Analysis of ORR, PFS rate and OS for SCCHN

Trial	N	ORR, % (95% CI)	PFS Rate, % (95% CI)		OS Rate, % (95% CI)	
			3 Mo	6 Mo	6 Mo	12 Mo
Fury et al. (2012)	Q2W = 35	11 (5, 26)	46 (30, 62)	14 (6, 30)	66 (49, 79)	26 (14, 43)
Kochanny et al. (2020)	Q2W = 38	8 (2, 21)	66 (50, 79)	24 (13, 40)	66 (50, 79)	26 (15, 42)
Ruzsa et al. (2014)	Q1W = 53	11 (5, 23)	62 (49, 74)	30 (19, 44)	NR	NR
Jimeno et al. (2014)	Q1W = 41	7 (2, 20)	NR	NR	NR	NR
Gilbert et al. (2015)	Q1W = 27	7 (2, 25)	50 (32, 68)	18 (8, 36)	64 (45, 80)	43 (26, 61)
Fayette et al. (2016)	Q1W = 62	15 (8, 26)	60 (47, 71)	26 (17, 38)	63 (50, 74)	36 (25, 48)
Pooled Q2W	73	10 (5, 19)	56 (44, 67)	20 (12, 31)	66 (54, 76)	26 (17, 37)
Pooled Q1W	184	11 (7, 17)	59 (50, 67)	26 (20, 34)	63 (53, 73)	38 (28, 48)

NR = not reported;

Source: Summarized from BLA 125084 s277, Clinical Study Report

SCCHN – Safety

Safety was analyzed for the cetuximab Q2W vs Q1W dosage regimens in patients with SCCHN in the meta-analysis. Results from the two pooled groups do not demonstrate a notable difference in the incidence of Grade 3-4 adverse events between groups (Table 10).

Table 10: Incidence Rate of Grade 3-4 Adverse Events in Published Literature of SCCHN

AEs (%)	Q2W Pooled		Q1W Pooled	
	N	Rate % (95% C)I	N	Rate % (95% CI)
Rash, acneiform	73	9 (4-18)	100	6 (2-14)
Fatigue	73	1 (0-9)	127	2 (0-7)
Hypomagnesemia	73	8 (3-19)	153	5 (2-10)
Nausea	73	4 (1-14)	NE	NE
Headache	NE	NE	NE	NE
Vomiting	73	4 (1-14)	NE	NE
Pyrexia	NE	NE	NE	NE
Dyspnea	NE	NE	153	7 (4-12)
Diarrhea	NE	NE	NE	NE

NE: not evaluated
Source: Clinical Overview submission

Cetuximab Formulations

There are different formulations of cetuximab marketed worldwide. The approved Erbitux (cetuximab) product in the EMA is manufactured and marketed by Merck Europe B.V., whereas the US-approved Erbitux (cetuximab) product is produced and manufactured by Eli Lilly (formerly by ImClone and Bristol-Myers Squibb). Section 12.3 (Pharmacokinetics) of current product labeling for Erbitux states: "The systemic exposure of cetuximab after Erbitux administration was 22% (90% CI: 6%, 38%) higher than that of another cetuximab product used in EXTREME and CRYSTAL"; the cetuximab product used in the EXTREME and CRYSTAL trial was produced in Europe, not the U.S.

Due to the use of different cetuximab formulations in US and ex-US locations, FDA requested specific information on the cetuximab formulations used in studies included in the aggregated analysis and in the Real World Evidence (RWE) study (described further in the section of the review entitled "Real-World Evidence for mCRC" below). Given that the literature search included only publicly available studies, the specific cetuximab formulation was not clearly described in the publications. However, most studies were conducted in the US, Canada, and the European Union. Eli Lilly previously conducted a randomized, double-blind study (Study I4E-MC-JXBD) of cetuximab administered using the same dosage regimen used in the EXTREME regimen, consisting of cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly in combination with platinum-based therapy (either carboplatin or cisplatin) and fluorouracil every 3 weeks for a maximum of 6 cycles, in approximately 200 patients with

recurrent/metastatic SCCHN. Patients were randomized (1:1) to receive either U.S. commercial cetuximab (Arm A) or Boehringer Ingelheim (BI)-manufactured cetuximab (European formulation, Arm B). The primary objective was to compare the safety profiles of the different cetuximab formulations and secondary objectives included ORR, PFS, and OS. Overall, the primary analyses showed no clinically meaningful differences in the safety profile of the two cetuximab formulations. Although the study was not powered for efficacy, no clinically meaningful differences in efficacy outcomes were observed between arms, despite the differences in formulation. Cetuximab manufacturing in Europe by BI was subsequently taken over by Merck KGaA which sponsored the studies included in the mCRC literature analysis as well as the CRYSTAL trial.

Of note, the RWE study (described in detail in a subsequent section of this review) was conducted using data from patients treated in the US who received the commercially available cetuximab formulation in the US (Erbitux produced by Eli Lilly).

Limitations of Aggregated Analyses from Published Literature for CRC and SCCHN

As discussed above, one potential limitation of the aggregated analyses from published literature relates to the potential use of different formulations of cetuximab in the published trials. However, these trials were primarily conducted in Europe, Canada, or the U.S. and results from Study I4E-MC-JXBD did not uncover material differences in safety or efficacy between the U.S-. and European manufactured cetuximab formulations, despite the 22% increase in exposure documented for the U.S.-produced product.

Additionally, patient-level data was not available for the literature-based analyses of the cetuximab Q2W dosage regimens for both mCRC and SCCHN so only pooled estimates for ORR, PFS landmark rate, and OS landmark rate can be reported to aggregate different study results. Censoring information for PFS and OS is not available and the aggregated analyses results are based on limited data extracted from literature publications. In addition, differences in ORR, PFS rates or OS rates between Q1W and Q2W treatment regimen cannot be evaluated for clinically relevant subgroups such as number of prior lines of systemic therapy, receipt of prior radiotherapy, age, or ethnicity.

Finally, patients with mCRC who were enrolled in the studies in which the Q2W regimen was used included various backbone chemotherapy combinations whereas patients in the cetuximab arm of the CRYSTAL study (cetuximab Q1W) received FOLFIRI. Therefore, the comparison between Q2W + FOLFIRI and Q1W + FOLFIRI is limited to only one study in which the Q2W regimen was administered (APEC). Despite this limitation, the estimates of the efficacy endpoints for the CRYSTAL and APEC studies are similar with largely overlapping confidence intervals.

Summary and Conclusions

The results of the aggregated analysis described in the preceding section are considered exploratory but provide additional support for the clinical pharmacology review team's

recommendation for approval of the Q2W dosage regimen for cetuximab for the mCRC and SCCHN indications as a single agent or in combination with chemotherapy .

Real World Evidence for mCRC

Eli Lilly conducted a retrospective observational comparative effectiveness study of real-world data (RWD) to compare survival outcomes of patients with K-Ras wild-type mCRC in the U.S. who received cetuximab Q2W vs Q1W. This analysis used the Flatiron Health electronic health record (EHR)-derived database and identified 23,681 patients with mCRC registered in the EHR between January 1, 2013 and December 31, 2019. This population of patients was further refined to those patients who were at least 18 years of age with Stage IV or recurrent mCRC who received cetuximab + FOLFIRI, cetuximab + FOLFOX, cetuximab + irinotecan or cetuximab monotherapy as first, second, or third line therapy. Additionally, patients must have had documented K-Ras wild-type status at any time prior to the index date or up to 30 days after the index date (the date of the initiation of cetuximab containing regimen). Of the initial 23,681 patients identified from the EHR database, 1074 met the above-mentioned criteria (with one patient, ID (b) (6), excluded due to a data error) and were included in the comparative analysis of OS. Of the population included in the comparative analysis, 61% of patients received the cetuximab Q1W and 39% of patients received the cetuximab Q2W dosing regimen. Due to lack of safety data in the Flatiron EHR database, a safety analysis was not performed.

Statistical Analysis Plan

OS was the only endpoint evaluated in the RWD analysis. A propensity score matching (PSM) method was used to balance the baseline demographic and clinical characteristics of patients receiving cetuximab Q2W and Q1W. Matching was completed using a 1:1 ratio and the propensity score model included age, gender, race, ethnicity, region, practice type, BMI, cancer stage at diagnosis, ECOG, mutation type, cancer site, NRAS mutation status, BRAF mutation status, backbone chemotherapy received, year of registered record (index date), time from initial diagnosis to index date, time from metastatic diagnosis to index date, and lines of therapy. After matching, overall survival was analyzed using a multi-variate Cox-proportional hazard model that included all covariates used in the propensity score model. Separate propensity score matched analyses were conducted for the overall population and by line of therapy. In the analysis of the overall population, line of therapy was treated as a categorical variable in the propensity score model.

Results

The baseline characteristics of the 1074 patients included for the OS analysis are reported in Table 11. Baseline characteristics before and after matching were provided. The standardized mean differences were also calculated. After matching, there were no major differences identified between matched patients who received the Q1W and Q2W regimens.

Table 11. Baseline Characteristics for Patients in the RWD Analysis

	Before Matching			After Matching		
	Q1W (N = 653)	Q2W (N = 421)	Standardized mean differences *	Q1W (N = 364)	Q2W (N = 364)	Standardized mean differences *
Age, Median	65	62	0.16	64	63	0.05
Male, N (%)	387 (59)	246 (58)	0.02	215 (59)	212 (59)	0.02
Race, N (%)						
White	434 (66)	288 (68)	0.04	250 (69)	246 (68)	0.02
Black or African American	56 (9)	33 (8)	0.03	26 (7)	32 (9)	0.06
Asian	25 (3.8)	15 (3.6)	0.01	17 (4.7)	14 (3.9)	0.04
Other or unknown	138 (21)	85 (20)	0.02	71 (20)	72 (20)	0.01
Ethnicity, N (%)						
Hispanic	86 (13)	32 (8)	0.18	32 (8.8)	31 (8.5)	0.01
Non-Hispanic	567 (87)	389 (92)		332 (91)	333 (91)	
Stage at diagnosis, N (%)						
I	10 (1.5)	4 (1.0)	0.05	5 (1.4)	4 (1.1)	0.02
II	46 (7)	50 (12)	0.17	34 (9)	37 (10)	0.03
III	192 (29)	121 (29)	0.01	108 (30)	135 (29)	0.16
IV	382 (59)	239 (57)	0.03	210 (58)	211 (58)	0.01
Unknown	23 (3.5)	7 (1.7)	0.12	7 (1.9)	7 (1.9)	0.00
Site at diagnosis, N (%)						
Colon	479 (73)	302 (71)	0.04	270 (74)	264 (73)	0.04
Rectum	162 (25)	110 (26)	0.03	86 (24)	92 (25)	0.04
Colorectal, not otherwise specified	12 (1.8)	9 (2.1)	0.02	8 (2.2)	8 (2.2)	0.00
Lines of therapy, N (%)						
1	226 (35)	146 (35)	0.00	130 (36)	124 (34)	0.03
2	292 (45)	185 (44)	0.02	155 (43)	162 (45)	0.04
3	135 (21)	90 (21)	0.02	79 (22)	78 (21)	0.01
ECOG						
0	166 (25)	130 (31)	0.12	110 (30)	102 (28)	0.05
1	174 (27)	130 (31)	0.09	115 (32)	113 (31)	0.01
2 or 3	62 (9)	39 (9)	0.01	36 (10)	33 (9)	0.03

	Before Matching			After Matching		
	Q1W (N = 653)	Q2W (N = 421)	Standardized mean differences *	Q1W (N = 364)	Q2W (N = 364)	Standardized mean differences *
Unknown	251 (38)	122 (29)	0.20	103 (28)	116 (32)	0.08
NRAS, N (%)						
Mutant	8 (1.2)	3 (0.7)	0.05	5 (1.4)	3 (0.8)	0.05
Wild-type	213 (33)	226 (54)	0.43	176 (48)	181 (50)	0.03
Unknown	432 (66)	192 (46)	0.42	183 (50)	180 (50)	0.02
BRAF, N (%)						
Mutant	28 (4.3)	18 (4.3)	0.00	18 (5.0)	17 (4.7)	0.01
Wild-type	220 (34)	208 (49)	0.32	163 (45)	163 (45)	0.00
Unknown	405 (62)	195 (46)	0.32	183 (50)	184 (51)	0.01
Time from initial diagnosis to index date, Months, Mean (SD)	22.8 (23.7)	24.4 (30.1)	0.32	24.4 (25.6)	24.2 (31.2)	0.05
Time from metastatic diagnosis to index date, Months, Mean (SD)	10.5 (10.1)	11.3 (11.7)	0.26	11.0 (11.0)	11.3 (11.3)	0.10

Source: FDA analysis on baselineos.sas7bdat, SDN 2005

* The standardized mean differences are calculated by method proposed by Zhang et al. 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6351359/)

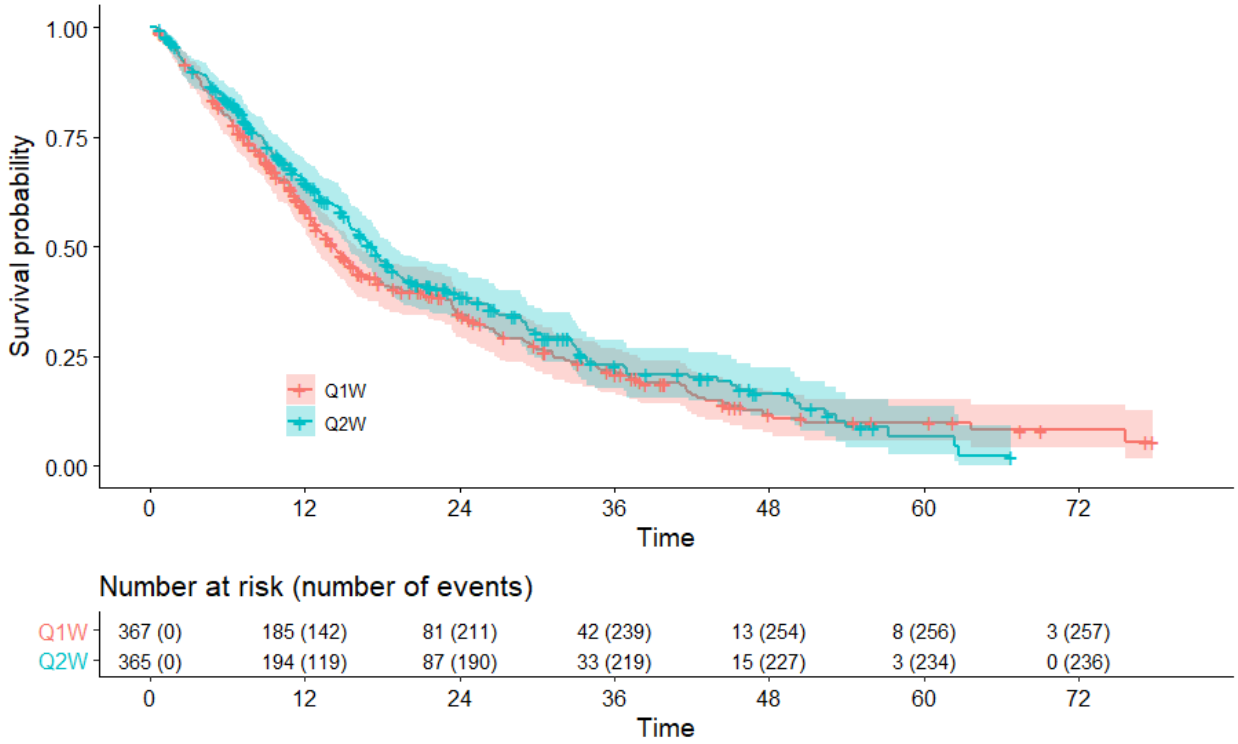
The efficacy results from the mCRC RWD analysis are displayed in Table 12. For the overall population, the difference in median OS is 2.9 months, favoring patients receiving the Q2W dosing schedule compared to patients receiving the Q1W regimen. For patients receiving cetuximab as first line therapy, the median OS is 5.8 months longer for patients receiving the Q2W regimen compared to patients receiving the Q1W regimen. The OS hazard ratios range from 0.86 to 0.97 for the comparison of dosing regimens by line of therapy and for the overall population; however, the 95% confidence intervals for all hazard ratios include the null value of 1, indicating that no evidence of a substantial difference in overall survival was observed between patients receiving the Q2W and Q1W regimens. The Kaplan-Meier curves for the overall population and subpopulation of patients receiving first line therapy are shown in Figure 1 and Figure 2, respectively. In both figures, the Kaplan-Meier curves for the Q2W and Q1W regimens overlap.

Table 12. Efficacy Results for mCRC RWD Analysis

Population	Dosing Schedule	N	Censoring Rate (%)	Median Overall Survival (95% CI), Months	HR (95% CI)
Overall	Q1W	364	30	14.32 (12.80, 16.02)	0.90 (0.75, 1.08)
	Q2W	364	35.4	17.24 (15.33, 18.82)	
First line	Q1W	121	38	23.36 (13.09, 32.17)	0.86 (0.62, 1.18)
	Q2W	121	40.5	29.14 (17.76, 36.91)	
Second line	Q1W	159	23.3	12.93 (11.05, 14.70)	0.92 (0.71, 1.19)
	Q2W	159	31.5	15.39 (11.94, 18.68)	
Third line	Q1W	70	24.3	12.53 (9.80, 15.56)	0.97 (0.65, 1.44)
	Q2W	70	32.9	12.83 (9.44, 15.53)	

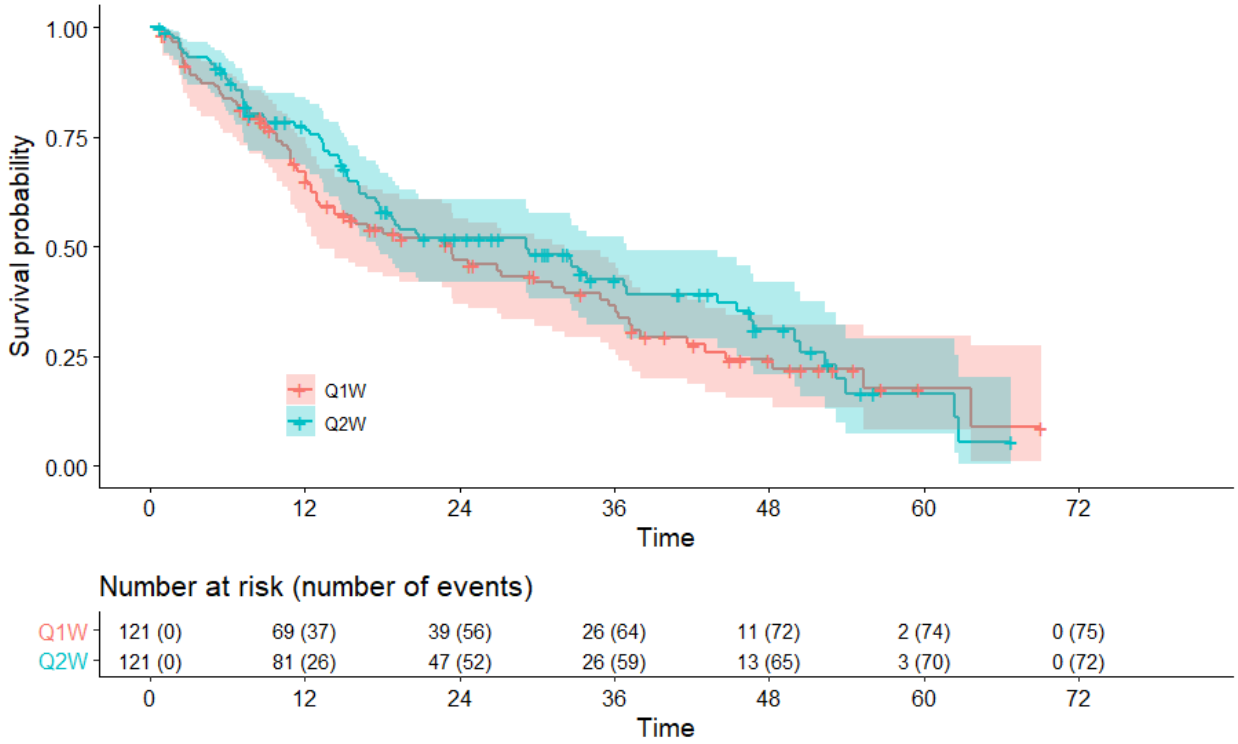
Source: Clinical Overview submission

Figure 1. Kaplan-Meier Curves of OS in RWD Analysis (all lines of therapy)



Source: FDA analysis on baselineos.sas7bdat, SDN 2005

Figure 2. Kaplan-Meier Curves of OS in RWD Analysis (first line therapy)



Source: FDA analysis on baselineos.sas7bdat, SDN 2005

In addition, FDA conducted two sensitivity analyses with variations in the set of variables included in the propensity score model. One sensitivity analysis limited the variables in the propensity score model to age, gender, race, ethnicity, region, practice type, BMI, cancer stage at diagnosis, ECOG, mutation type, lines of therapy. The second sensitivity analysis included all the variables in the primary propensity score model except for the index date. The results of both sensitivity analyses were similar to the results of the primary RWD analysis.

Statistical Considerations and Limitations of the RWD analysis

The Q1W cohort includes patients who received 70% or more of the planned cetuximab doses within 4-10 days from the previous administration and the Q2W cohort includes patients who received 70% or more of the planned cetuximab doses within 11-18 days from the previous administration. The median dosage of cetuximab was 246.1 mg/m^2 (range: 112.0-336.1 9 mg/m^2) for the Q1W cohort and 484.9 mg/m^2 (range: 185.0-532.7 mg/m^2) for the Q2W cohort in the overall population. The median time gap between subsequent cetuximab administrations was 7 days (range: 1-756 days, 5% quantile: 7 days, 95% quantile: 14 days) in the Q1W cohort and 14 days (range: 1-527 days, 5% quantile: 13 days, 95% quantile: 28 days) in the Q2W cohort. Given the range of dosing time intervals for patients in the Q1W cohort and the Q2W cohort, the Q1W or Q2W cohorts do not include only those patients received cetuximab exactly every 7 days or every 14 days, respectively. As a result, the true differences between the Q1W and Q2W regimens may be slightly different than estimated in this analysis. However, the

observed range of time intervals between cetuximab doses for Q1W and Q2W regimen is not unexpected and likely to be consistent with how cetuximab is administered in the post-market setting.

Statistical methods, which in this case was propensity score matching, cannot entirely resolve the issues of selection bias and confounding variables that are intrinsic to observational data, particularly with respect to unmeasured or mis-specified factors. Also, while overall survival as an endpoint is generally considered to be an appropriate endpoint for a randomized study, missing death data in real-world data may lead to incomplete capture of events, depending on the data used for confirmation of survival status. In this case, misspecification or inaccurate data on the endpoint could lead to biased results, particularly if this is linked to treatment groups. Though this is unlikely to be the case, in an observational and retrospective analysis, this possibility cannot be completely ruled out.

In addition, because patient-level information regarding prior lines of treatment was not available, FDA could not independently verify that the line of therapy assigned to each patient was accurate. Although the real-world data analyses are considered exploratory, despite the above-mentioned limitations, the FDA clinical and statistical review teams considered these analyses generally supportive of the clinical pharmacology assessment and recommendation for approval of the Q2W dosage regimen.

Clinical and Statistical Review Team Assessment and Recommendation:

There was no substantial difference in the efficacy outcomes or the safety profiles between the Q1W and Q2W cetuximab dosing regimens in either meta-analysis. Additionally, despite the limitations of the real-world data, the RWD analysis was also supportive of this finding. The clinical and statistical review teams concluded that based on these results, the Q2W dosage regimen for cetuximab, as a single agent or in combination with cytotoxic chemotherapy, is unlikely to result in differences in the efficacy and safety compared to the Q1W dosing regimen in patients with SCCHN or mCRC. Therefore, the clinical and statistical teams recommend approval of the Q2W dosage regimen.

CDTL Review

Cetuximab is a human/mouse chimeric monoclonal immunoglobulin G1 antibody directed against EGFR. It is approved for use in *K-Ras* wild-type, EGFR-expressing mCRC and SCCHN at an initial dose of 400 mg/m^2 followed by weekly (Q1W) doses of 250 mg/m^2. With this application, Eli Lilly has provided pharmacokinetic (PK) modeling data as well as a population PK (popPK) analysis to support a biweekly dosage regimen of cetuximab for use in mCRC and SCCHN of 500 mg/m^2 administered Q2W. The clinical pharmacology data is supported by an aggregate analysis of published clinical studies in which cetuximab was administered Q2W in patients with mCRC and SCCHN. In addition, Eli Lilly conducted a retrospective observational comparative effectiveness study of RWD to compare survival outcomes of patients with K-Ras wild-type

mCRC in the U.S. who received cetuximab Q2W vs Q1W, which also provides supportive evidence for the proposed dosing regimen.

This application is primarily supported by results of PK modeling analyses comparing the two dosage regimens. The concentration-time profiles of cetuximab at the Q1W and Q2W dosage regimens overlap and the predicted Cavg at steady state of the two dosage regimens is comparable. The Cmin at steady state of the Q2W cetuximab dosing regimen is approximately 23-25% lower than that of the Q1W dosing regimen in patients with SCCHN and mCRC; however, the clinical pharmacology review team analyses showed that on average, only approximately 6% of patients who receive 500 mg/m^2 Q2W would have a cetuximab concentration below the lower bound of the 90% confidence interval (CI) of Cmin, ss at 250 mg/m^2 QW and that for those patients, this lower Cmin would last for only approximately 1-2 days out of the 2-week dosing interval, which is unlikely to be of clinical consequence. Furthermore, the difference in Cmin is likely to be ameliorated by the observed 22% increase in systemic exposure with the Eli Lilly-produced commercial product compared to the product used in the clinical trials (CRYSTAL and EXTREME) supporting the original mCRC and SCCHN indications. When adjusting for the exposure difference between the Eli Lilly-produced Erbitux commercial product and the cetuximab product used in the CRYSTAL and EXTREME trials supporting the mCRC and SCCHN indications, respectively, a smaller difference in Cmin is expected (Cmin projected to be approximately 15% lower for the Q2W regimen compared to the Cmin observed for the Q1W regimen for the product used in the pivotal trials).

In addition, there was not a notable difference in biomarker responses such as downregulation of phospho(p)-EGFR, p-MAPK and proliferation and upregulation of p27Kip1 and p-STAT3 levels in paired skin samples from 35 patients among different dose levels, which provided further support for the proposed 500 mg/m^2 Q2W dosing regimen. The geometric mean of steady-state Cmax achieved with 500 mg/m^2 Q2W is approximately 50% higher than that with the 250 mg/m^2 QW regimen; however, in Study EMR 62202-045, a clinical trial evaluating dosages of cetuximab, dosages up to 700 mg/m^2 Q2W were evaluated without identification of a maximum tolerated dose and the safety profiles appeared similar across the dosage ranges.

Supportive clinical data includes an analysis of published results from clinical trials in patients with mCRC and SCCHN in which pooled estimates for ORR, PFS landmark rate, and OS landmark rate were similar between Q2W and Q1W dosing regimens. For mCRC, the ORR observed in patients enrolled in the APEC study, in which cetuximab Q2W was administered in combination with FOLFIRI, was 55% (95% CI 44, 64), compared to 57% (95% CI: 52-63) in the CRYSTAL study, which supported approval of the cetuximab Q1W regimen in combination with FOLFIRI. Comparisons of PFS rates at 6, 12, and 18 months, and OS rates at 6, 12, 24, and 36 months for patients with mCRC in the pooled Q2W cohort compared to patients enrolled in the CRYSTAL study were also similar, with overlapping confidence intervals at all timepoints.

The meta-analyses for SCCHN were less robust given the relatively small patient samples sizes; however, the ORR, landmark PFS rates at 3 months and 6 months, and landmark OS rates at 6 and 12 months were numerically similar, and the 95% confidence intervals overlapped across

the pooled analysis of patients who received cetuximab Q2W and those who received cetuximab Q1W. The ORR observed for the pooled Q2W cohort was 10% (95% CI 5, 19) compared to 11% (95% CI 7, 17) for the pooled Q1W cohort; PFS rates at 6 months were 20% (95% CI 12, 31) and 26% (95% CI 20, 34), respectively. The 6-month OS rate for the pooled Q2W cohort was 66% (95% CI: 54, 76) compared to 63% (95% CI: 53,73) in the pooled Q1W cohort and the 12-month OS rates were 26% (95% CI: 17, 37) and 38% (95% CI: 28, 48), respectively. Safety data, including rates of Grade 3-4 adverse events, were also comparable between the two regimens for both mCRC and SCCHN patients.

The RWD study with propensity score matching compared patients with mCRC who received cetuximab Q1W and cetuximab Q2W as various lines of therapy with a primary efficacy outcome measure of OS. Overall, the median OS in patients receiving the Q2W regimen was 17.2 months (95% CI 15.3, 18.8) compared to 14.3 months (95% CI 12.8, 16.0), with a hazard ratio of 0.90 (95% CI 0.75, 1.08). These results are similar with the confidence interval around the hazard ratio crossing one.

In summary, using a MIDD approach, Lilly conducted PK modeling and simulations based on clinical data to compare the PK profile of the currently approved Q1W dosing schedule with that of the proposed 500 mg/m^2 Q2W dosing schedule. In both the observed clinical data from Study EMR 62202-045 and the simulated PK profiles in patients with CRC and SCCHN, the overall cetuximab PK profiles between the 2 dosing schedules are generally comparable. As supportive clinical evidence, Lilly conducted an analysis of published clinical data and a retrospective observational study using RWD to compare the efficacy and safety of the approved Q1 and proposed Q2 dosing schedules. In the aggregate analysis, the clinical outcomes in both efficacy and safety observed between the two dosing schedules in patients with mCRC and SCCHN were similar. The efficacy outcomes from the RWD analyses were also similar between the approved Q1 and proposed Q2 dosing schedules in patients with mCRC. Therefore, based on the totality of evidence provided to support this sBLA, the clinical and statistical review teams concur with the Office of Clinical Pharmacology's recommendation for approval of the cetuximab 500 mg/m^2 Q2W dosage regimen for the approved indications for CRC and SCCHN either as a single agent or in combination with chemotherapy.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANICE H KIM
04/06/2021 12:45:06 PM

XIAOXUE LI
04/06/2021 12:53:34 PM

YUAN L SHEN on behalf of PALLAVI S MISHRA-KALYANI
04/06/2021 01:48:24 PM

NICOLE L DREZNER
04/06/2021 01:59:33 PM

YUAN L SHEN
04/06/2021 02:00:37 PM

MARTHA B DONOGHUE
04/06/2021 02:03:31 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084Orig1s277, s280

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	125084 S277 and 280.
Subject:	Efficacy supplement, Labeling change to allow for biweekly dosing of cetuximab.
Stamp Date:	19 Nov 2020.
Review/Revision Date:	9 March 2021.
Primary Reviewer:	Ralph M. Bernstein.
Secondary Reviewer:	Chana Fuchs.
RBPM:	Kristine Leahy.
Consults:	N/A.
Applicant:	Eli Lilly and Company.
Product:	Erbitux- cetuximab.
Indication:	Squamous Cell Carcinoma of the Head and Neck (SCCHN) (S-280) and Colorectal Cancer (CRC) (S-277)
Filing Action Date:	17 Jan 2021
Action Due Date:	19 September 2021

1. Summary Basis of Recommendation:

a. Recommendation: approval.

b. Justification: The applicant's quality data supports the safety of the proposed change. Applicant also updated the PI based on the requests from CMC for the relevant items

2. Suggested Language for Action Letter: Defer to clinical.

3. Review:

The applicant has submitted a Prior Approval Labeling Supplement to seek approval for the addition of a biweekly dosing schedule to the Erbitux® (cetuximab) USPI. The proposed biweekly (Q2W) dosage for Erbitux for use in metastatic Colorectal Cancer (mCRC) and in recurrent/metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN) is proposed to be 500 mg/m2 administered as 120-minute intravenous infusion.
Because of the two different indications, the original supplement 277 was broken into two efficacy PASs, 277 and 280 for CRC and for SCCHN , respectively.

Dosage and Administration in the USPI has been modified to the following (changes in italics).

Administer Weekly: 400 mg/m^2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m^2 weekly infused over 60 minutes or *Biweekly: 500 mg/m^2 administered as a 120-minute intravenous infusion every two weeks*.

This CMC review consists of a safety evaluation and a change to the labeling text to make the preparation section of the label current regarding the presence of particulate matter or if the vial is cloudy:

Safety:
1--Potential endotoxin exposure:
Using the Mosteller body surface area (BSA) calculation, as found at:
https://reference.medscape.com/calculator/692/body-surface-area-based-dosing

--for a 6' tall 200 pound (90kg) individual, total cetuximab dose would be 1073.37 mg over 120 min, which is 536 mg/hour. The maximum level for endotoxin safety is 5EU/kg/hour for IV or IM route of administration. The release specification for cetuximab DP is ≤ (b) (4) EU/mg. Therefor, for the theoretical 6' tall 200lb (90kg) individual the theoretical exotoxin exposure would be (total dose 536mg/hr. Theoretical maximum endotoxin therefore (b) (4) EU total. 90kg/ (b) (4) EU= (b) (4) EU/kg/hour which is well within the limit of 5EU/kg/hour.

2--Potential DNA exposure: WHO (b) (4) ng/dose. Release specification for cetuximab DS is <= (b) (4) g/mg protein. Which is ((b) (4) mg* (b) (4) pg= (b) (4) pg) (b) (4) ng maximum theoretical dose for the the retical 6 foot tall, 200lb individual. This is well withing the (b) (4) ng/dose limit.

Environmental assessment: an EA section was not included in the submission. An IR was sent to applicant who subsequently submitted an appropriate waiver in an amendment to this supplement.

Suggested appearance labeling change:
The agency recommended that the applicant alter section 2.5 of the label to include "Do not use if solution is discolored, cloudy, or contains foreign particulate matter."
This fact seems to have been dropped/modified through the many revisions and labeling history of the product.
The applicant accepted the proposed change:

2.5 Preparation for Administration

- 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.
- Visually inspect for foreign particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is discolored, cloudy, or contains foreign particulate matter.

4. Reviewer conclusions:

Supplement 277 and 280 are approvable from a product quality perspective, as there are no CMC safety concerns.

5. Future Inspection Items: None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARYAM M KHAZRAEE
03/29/2021 12:37:06 PM

RALPH M BERNSTEIN
03/29/2021 03:48:18 PM

CHANA FUCHS
03/30/2021 12:28:34 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084Orig1s277, s280

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	BLA 125084/S-277& S-280
Link to EDR	\\CDSESUB1\evsprod\BLA125084\0593
Submission Date	Nov 19, 2020
Submission Type	Standard
Brand Name	ERBITUX
Generic Name	Cetuximab
Formulation	Injection: 100 mg/50 mL (2 mg/mL) or 200 mg/100 mL (2 mg/mL) in a single-dose vial
Route of Administration	Intravenous infusion
Proposed Dosing Regimen	Adding an alternate biweekly dosing regimen of 500 mg/m^2 administered as a 120-minute intravenous infusion
Proposed Indications	• K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer • squamous cell carcinoma of the head and neck
Applicant	Eli Lilly and Company
OCP Review Team	Youwei Bi, Ph.D.; Jiang Liu, Ph.D.; Vicky Hsu, Ph.D.; Hong Zhao, Ph.D.

1. Executive Summary

Cetuximab is a human/mouse chimeric monoclonal immunoglobulin G1 antibody specifically directed against the epidermal growth factor receptor (EGFR). Erbitux (cetuximab) is approved for use in K-Ras wild type, EGFR-expressing metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and neck (SCCHN) at an initial dose of 400 mg/m^2 administered as a 120-minute intravenous infusion followed by weekly (QW) doses of 250 mg/m^2 administered as a 60-minute intravenous infusion.

In the current submission, the applicant proposes to add new biweekly dosing regimen of cetuximab 500 mg/m^2 administered as a 120-minute intravenous infusion to the currently approved indications based on results of PK comparison, meta-analyses and real-world evidence. OCP has completed the review and concludes that the available clinical pharmacology and clinical data provide sufficient evidence to support the approval of the proposed cetuximab dosing regimen of 500 mg/m^2 Q2W.

In summary, the concentration-time profiles of cetuximab at QW and Q2W dosing regimens are overlapping and the predicted Cavg at steady state of the two dosing regimens are comparable. The Cmin at steady state of Q2W cetuximab dosing regimen is around 23-25% lower compared to that of QW dosing regimen in patients with SCCHN and mCRC. Although limited by small number of subjects per dose group, the safety profiles and biomarkers related to EGFR levels in the Phase 1 dose-escalation study (EMR 62202-045) appear to be comparable across dose levels ranging from 400 to 700 mg/m^2 Q2W. In addition to the comparative clinical pharmacology findings including PK, safety profile and biomarkers related to EGFR levels between these two cetuximab dosing regimens, meta-analyses of clinical trials, as well as the real-world evidence, comparing efficacy and safety between Q2W and QW dosing regimens are also provided to address the residual uncertainty and support the approval of Q2W dosing regimen (please see clinical review).

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information in the supplemental BLA and recommends approval of the alternate cetuximab dosing regimen of 500 mg/m^2 Q2W for all approved indications.

1.2. Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments are requested from a clinical pharmacology perspective.

Signatures:

Youwei Bi, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Jiang Liu, Ph.D. Pharmacometrics Team Leader Division of Pharmacometrics
Vicky Hsu, Ph.D. Clinical Pharmacology Reviewer Division of Cancer Pharmacology I	Hong Zhao, Ph.D. Clinical Pharmacology Team Leader Division of Cancer Pharmacology I

2. Clinical Pharmacology Questions

Is the proposed 500 mg/m^2 Q2W dosing regimen supported by clinical pharmacology findings?

Yes, the available clinical pharmacology findings together with clinical findings provide sufficient evidence for the approval of the proposed dosing regimen of 500 mg/m^2 Q2W.

The model prediction based on a previously developed popPK model was shown to well describe the observed cetuximab PK data in the phase 1 dose-escalation study EMR 62202-045. The concentration-time profiles of cetuximab Q2W and QW regimens are overlapping and predicted Cavg at steady state are comparable between Q2W and QW dosing regimen (with 5-6% prediction variability) (Figure 1). The geometric mean of steady-state cetuximab Cmin (Cmin,ss) achieved with 500 mg/m^2 Q2W is 25% and 23% lower compared to QW dosing regimen in patients with SCCHN and mCRC (Table 1), respectively. A Phase 1 dose-escalation study (EMR 62202-045) was conducted to determine the maximum tolerated dose (MTD) and recommended dose of cetuximab administered on Q2W schedule to patients with mCRC. In the dose-escalation group, new patients received cetuximab at 400, 500, 600 or 700 mg/m^2 Q2W.The observed PK data from study EMR 62202-045 showed a 37% lower Cmin,ss comparing 500 mg/m^2 Q2W to 250 mg/m^2 QW regimen. The numerical discrepancy in Cmin,ss between calculation based on observed PK data (37%) and predication from simulation (23-25%) is probably due to the small number of patients in study EMR 62202-045 and is within the random between patient variability.

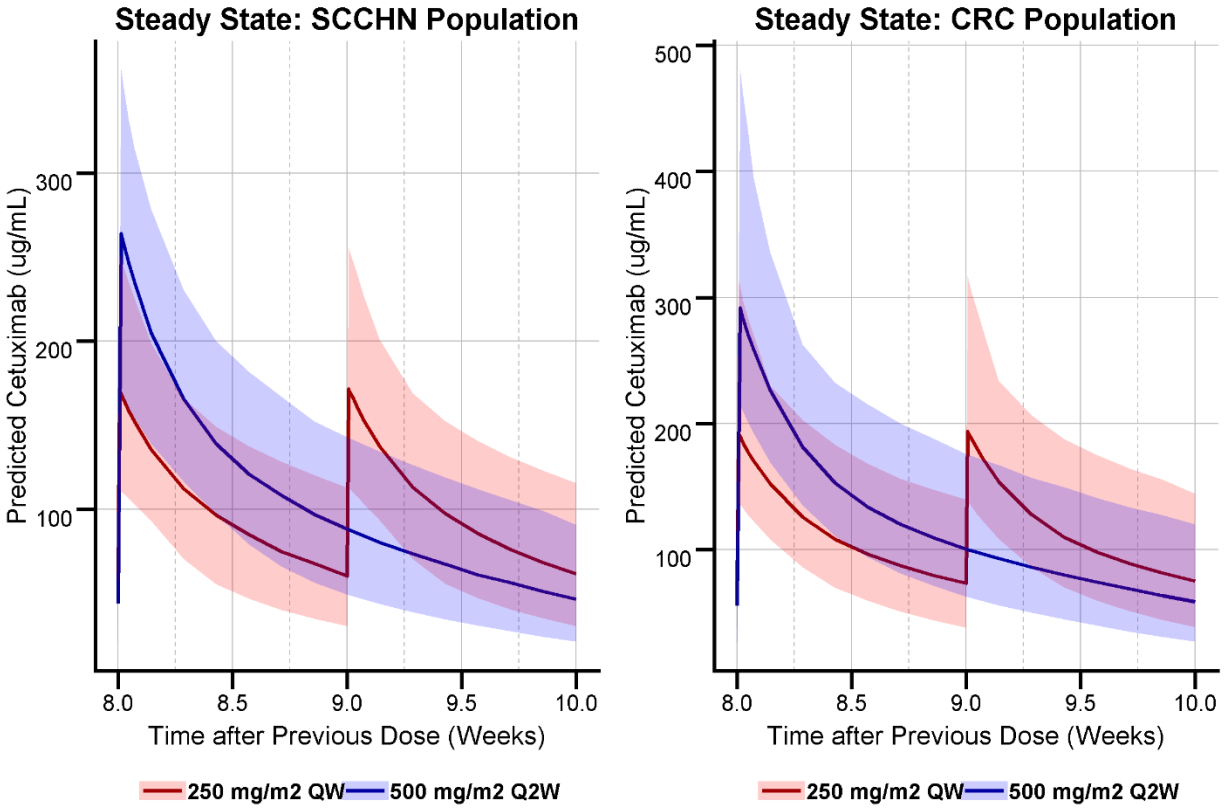
To further evaluate the potential impact of the lower Cmin,ss of Q2W dosing regimen, the duration of time at steady state where the proposed 500 mg/m^2 Q2W dosing regimen would have concentrations lower than that of 250 mg/m^2 QW was estimated. The estimation shows that, on average, approximately 6% of the patients who received 500 mg/m^2 Q2W dosing regimen would have their concentrations below the lower bound of 90% confidence interval (CI) of Cmin,ss at 250 mg/m^2 QW for approximately 1-2 days out of the 2-week dosing interval and is unlikely to be of clinical consequence. In addition, no marked difference was observed on biomarker responses (downregulation of phospho(p)-EGFR, p-MAPK and proliferation and upregulation of p27Kip1 and p-STAT3 levels) in paired skin samples from 35 patients among different dose levels, which provided further support for the proposed 500 mg/m^2 Q2W dosing regimen.

The geometric mean of steady-state Cmax achieved with 500 mg/m^2 Q2W is about 50% higher than that with 250 mg/m^2 QW. However, the MTD of cetuximab tested up to 700 mg/m^2 Q2W

was not reached, and the safety profiles appeared to be similar across all dose groups (about 12 patients per group) in the phase 1 study EMR 62202-045.

Overall, the concentration-time profiles of QW and Q2W dosing regimens are overlapping and the predicted Cavg at steady state of the two dosing regimens are comparable. The Cmin,ss of Q2W is 23-25% lower than that of QW dosing regimen in SCCHN and mCRC patients. Although limited by small number of patients per dose group, the safety profiles and biomarkers related to EGFR levels appear to be comparable across different dose levels in the Phase 1 study EMR 62202-045. In addition to the comparable clinical pharmacology data between these two dosing regimens, clinical meta-analyses, as well as the real-world evidence, comparing efficacy and safety between Q2W and QW dosing regimens are also provided to support the Q2W dosing regimen (please see clinical review)

Figure 1: Predicted Geometric Mean (with 95% CI) Cetuximab Concentration-Time Profiles (Steady-State), by Dosing Regimen (250 mg/m^2 QW and 500 mg/m^2 Q2W) in 526 patients with mCRC or 173 patients with SCCHN.



Note: Solid colored lines: geometric mean; Shaded Areas: 95% confidence intervals

Source: Reviewer's independent analysis based on previously developed popPK model (Report Number RAIMC00100)

3. Appendix

3.1. Population Pharmacokinetic Analysis

The goal of popPK analysis was to apply popPK model to predict the cetuximab exposure produced by 500 mg/m^2 Q2W and 250 mg/m^2 QW in patients with SCCHN or mCRC.

A previous popPK analysis included more than 8300 cetuximab concentration observations in 906 patients (173 SCCHN patients and 526 mCRC patients) from 19 studies. The cetuximab doses used in these studies ranged from 5 to 500 mg/m^2 and up to 500 mg/m^2 QW administration. The final population model was a two-compartment model with saturable elimination. The popPK model was previously reviewed by the agency and found acceptable to describe the observed data. To further qualify the above popPK model, the simulated concentration-time profiles were compared with the observed data from study EMR 62202-045 in patients with mCRC. As shown in Figure 2, the model prediction matched the observed data fairly well, suggesting that the previously developed popPK model is acceptable in predicting the cetuximab exposure across the QW and Q2W dosing regimens.

The model was then applied to simulate the cetuximab exposure produced by 500 mg/m^2 Q2W and 250 mg/m^2 QW in 526 patients with mCRC or 173 patients with SCCHN. Independent analysis was conducted by the reviewer to confirm applicant's results. The simulation results show a large overlap of the cetuximab concentration profiles at steady state between the two dosing regimens in patients with mCRC or SCCHN. The geometric mean of steady-state Cavg achieved with cetuximab 500 mg/m^2 Q2W and 250 mg/m^2 QW is comparable (with 5-6% prediction variability). The geometric mean of steady-state Cmax achieved with cetuximab 500 mg/m^2 Q2W is about 50% higher compared to 250 mg/m^2 QW. The geometric mean of steady-state Cmin achieved with cetuximab 500 mg/m^2 Q2W is 25% and 23% lower compared to QW dosing regimen in patients with SCCHN and mCRC, respectively. These simulation results are comparable with the applicant's results where Cmin,ss of 500 mg/m^2 Q2W is 26-30% lower than that of 250 mg/m^2 QW in patients with mCRC and SCCHN. Minor numerical difference was observed probably due to the difference in the simulation datasets.

In the phase 1 dose-escalation study EMR 62202-045, patients with mCRC received cetuximab either at the labeling recommended dosing regimen or at 400, 500, 600 or 700 mg/m^2 Q2W. Observed PK data showed 37% lower Cmin,ss and 43% higher Cmax,ss comparing 500 mg/m^2 Q2W to 250 mg/m^2 QW regimen. The numerical discrepancy in Cmin,ss between calculation based on observed PK data (37%) and predication from simulation (23-25%) is probably due to the small number of patients in study EMR 62202-045 and is within the random between patient variability.

To further evaluate the potential impact of the lower Cmin,ss of Q2W dosing regimen, the duration of time at steady state where the proposed 500 mg/m^2 Q2W dosing schedule would have concentrations lower than that of 250 mg/m^2 QW was estimated. The estimation shows that, on average, approximately 6% of the patients who received Q2W dosing regimen would have their concentrations below the lower bound of 90% CI of Cmin,ss at 250 mg/m^2 QW for approximately 1-2 days out of the 2-week dosing interval.

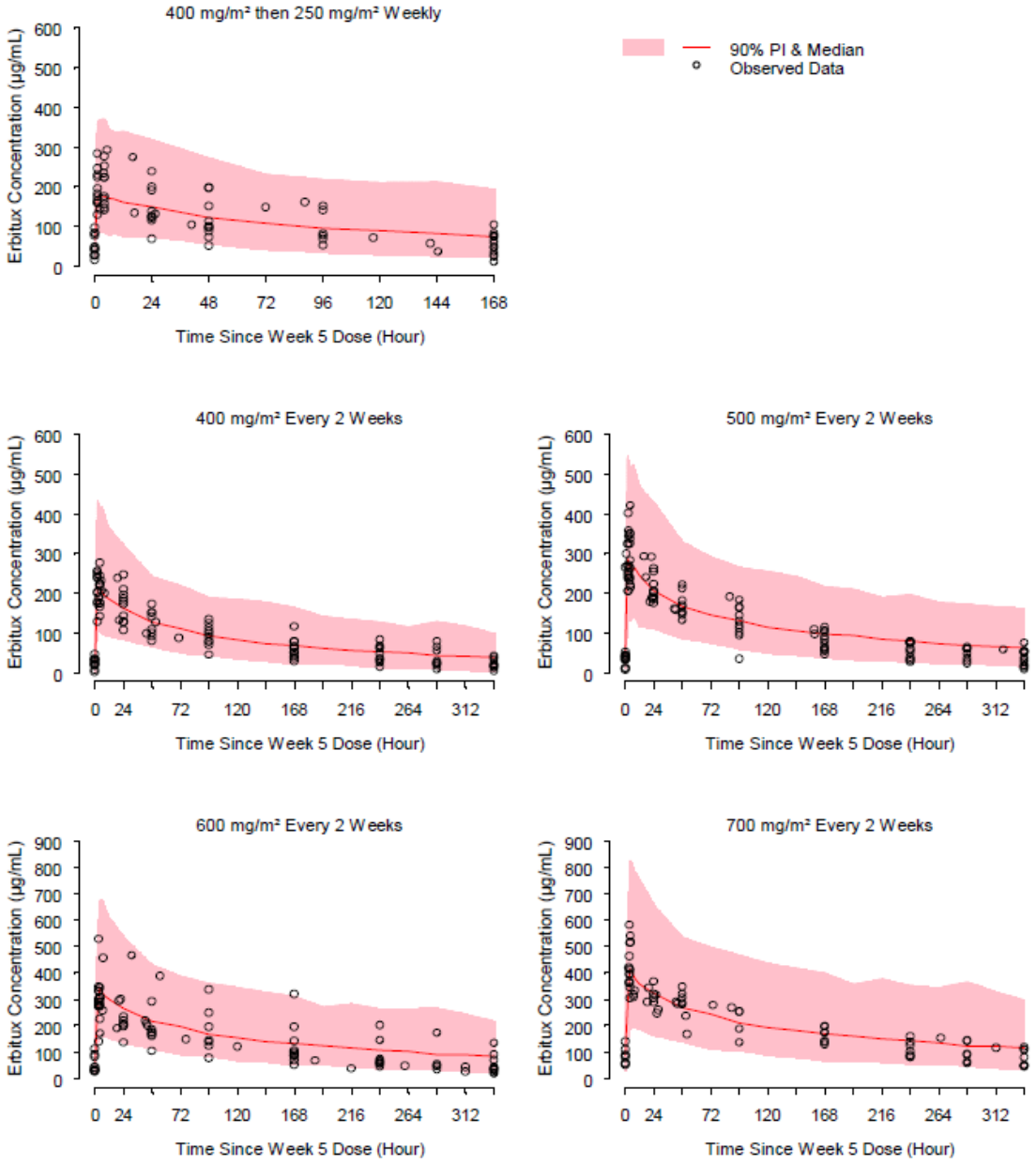
Table 1: Summary of Geometric Mean Exposure for Cetuximab 250 mg/m^2 QW and 500 mg/m^2 Q2W in Patients with mCRC or SCCHN

Cancer	Exposure (ug/mL)	250 mg/m^2 QW	500 mg/m^2 Q2W	Time	Difference (%)
SCCHN	Cavg	98.74	105.02	SS	6.4
SCCHN	Cmax	172	262.4	SS	52.6
SCCHN	Cmin	62.38	46.87	SS	-24.9
mCRC	Cavg	113.91	120.1	SS	5.4
mCRC	Cmax	196.3	296.14	SS	50.9
mCRC	Cmin	75.1	57.98	SS	-22.8

Difference: 500 mg/m^2 Q2W vs 250 mg/m^2 QW

Source: Reviewer's independent analysis based on previously developed popPK model (Report Number RAIMC00100)

Figure 2: Comparison between observed data from Study EMR 62202-045 and simulated cetuximab concentration-time profiles at Week 5 in patients with mCRC after receiving the standard 400 mg/m^2 followed by 250 mg/m^2 QW or a 400 mg/m^2, 500 mg/m^2, 600 mg/m^2, or 700 mg/m^2 Q2W dosing regimen.



Note: The red median line and shaded areas represents the median and variability from the simulation; The black dots are observed data from phase 1 trial EMR 62202-045.

Source: Applicant Clinical Overview, Figure 2.5.3-1, Page 22

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YOUWEI N BI
03/29/2021 09:28:38 AM

JIANG LIU
03/29/2021 09:30:49 AM

WENCHI HSU
03/29/2021 10:21:31 AM

HONG ZHAO
03/29/2021 12:16:09 PM
concur.

NAM ATIQUR RAHMAN
03/29/2021 12:33:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125084Orig1s277, s280

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 22, 2021

To: Maryam Khazraee, PharmD, BCPS, Regulatory Project Manager
Division of Oncology 3 (DO3)

From: Emily Dvorsky, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ERBITUX® (cetuximab) injection, for intravenous use

BLA: 125084/Supplement 277

In response to DO3's consult request dated January 11, 2021, OPDP has reviewed the proposed product labeling (PI) for ERBITUX® (cetuximab) injection, for intravenous use. This supplement (S-277) provides for the addition of a new dosing schedule.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Maryam Khazraee) on March 18, 2021, and we have no additional comments at this time.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

20 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY M DVORSKY
03/22/2021 10:01:31 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 1, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 125084 S-277
Product Name, Dosage Form, and Strength:	Erbitux (cetuximab) injection, 100 mg/50 mL (2 mg/mL) and 200 mg/100 mL (2 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company (Eli Lilly)
FDA Received Date:	November 19, 2020
OSE RCM #:	2021-90
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

Eli Lilly and Company (Eli Lilly) submitted BLA 125084 Prior Approval Supplement (PAS) 277 for Erbitux (cetuximab) injection to seek approval for the addition of a biweekly dosing schedule to the Erbitux prescribing information (PI). This review responds to the January 11, 2021 Division of Oncology 3 (DO3) consult for DMEPA to evaluate the proposed changes to the Erbitux PI for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Erbitux PI and note the biweekly dosing regimen added to Section 2. We find the edits acceptable from a medication safety perspective but have one minor recommendation for the Dosage and Administration section of the Highlights provided in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Erbitux PI Highlights Dosage and Administration section may be improved to promote the safe use of the product as described in Section 4.1.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Highlights Dosage and Administration Section

a. We recommend adding “radiation therapy” to the last bullet in order to match the dosing instructions provided in Section 2 of the full PI, as follows:

- “(b) (4) Complete ERBITUX administration 1 hour prior to radiation therapy, (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Erbitux received on November 19, 2020 from Eli Lilly and Company (Eli Lilly).

Table 2. Relevant Product Information for Erbitux	
Initial Approval Date	February 12, 2004
Proper Name	cetuximab
Indication	Erbitux is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of: <u>Head and Neck Cancer</u> • Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy. • Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil. • Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. <u>Colorectal Cancer</u> K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by an FDA-approved test • in combination with FOLFIRI for first-line treatment, • in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy, • as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan. Limitations of Use: ERBITUX is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.
Route of Administration	intravenous
Dosage Form	injection
Strength	100 mg/50 mL (2 mg/mL) and 200 mg/100 mL (2 mg/mL)
Dose and Frequency	Recommended Dosage for Squamous Cell Carcinoma of the Head and Neck (SCCHN): <u>In combination with radiation therapy</u> (b) (4) [redacted]

	(b) (4) • Complete ERBITUX administration 1 hour prior to radiation therapy. As (b) (4) or in combination with platinum-based therapy and fluorouracil (b) (4) Weekly • Initial dose: 400 mg/m^2 administered as a 120-minute intravenous infusion • Subsequent (b) (4): 250 mg/m^2 administered as a 60-minute infusion every week Biweekly • 500 mg/m^2 administered as a 120-minute intravenous infusion every 2 weeks Complete ERBITUX administration 1 hour prior to platinum-based therapy with fluorouracil. Continue treatment until disease progression or unacceptable toxicity. Recommended Dosage for Colorectal Cancer (CRC) (b) (4) Weekly • Initial dose: 400 mg/m^2 administered as a 120-minute intravenous infusion • Subsequent (b) (4): 250 mg/m^2 administered as a 60-minute infusion every week Biweekly • 500 mg/m^2 administered as a 120-minute intravenous infusion every 2 weeks Complete ERBITUX administration 1 hour prior to irinotecan or FOLFIRI. Continue treatment until disease progression or unacceptable toxicity. See Table 1 for Recommended Dosage Modifications for Adverse Reactions

How Supplied	ERBITUX (cetuximab) injection is a sterile, preservative-free, clear, colorless solution in a 2 mg/mL single-dose vial supplied as follows: • 100 mg/50 mL individually packaged in a carton (NDC 66733-948-23) • 200 mg/100 mL individually packaged in a carton (NDC 66733-958-23)
Storage	• Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). • Do not freeze or shake. • Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C.
Container Closure	vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 10 and 11, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Erbitux, cetuximab, and BLA# 125084. Our search identified one previous review[a], and we confirmed that our previous recommendations were implemented.

[a] Duffy, F. Label and Labeling Review for Erbitux (cetuximab), BLA 125084. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 AUG 17. RCM No.: 2006-172 and 2009-1007.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Erbitux labeling submitted by Eli Lilly and Company (Eli Lilly).

- Prescribing Information (Image not shown) received on November 19, 2020, available from \\CDSESUB1\evsprod\bla125084\0593\m1\us\proposed-uspi.docx.

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARAH E THOMAS
03/01/2021 10:51:43 AM

ASHLEIGH V LOWERY
03/03/2021 04:55:28 PM