ERBITUX, in combination with radiation therapy, is approved for the initial treatment of a certain type of locally or regionally advanced head and neck cancer.

ERBITUX, in combination with platinum-based chemotherapy with 5-fluorouracil, is approved for the initial treatment of patients with a certain type of head and neck cancer whose tumor has returned in the same location or spread to other parts of the body.

ERBITUX is also approved for use alone to treat patients with a certain type of head and neck cancer whose tumor has returned in the same location or spread to other parts of the body and whose disease has progressed following platinum-based chemotherapy.

ERBITUX is available by prescription only.

WARNING: ALLERGIC REACTIONS and HEART ATTACK

Allergic Reactions
- Severe allergic reactions due to ERBITUX® (cetuximab) therapy have occurred in 42 of 1373 patients (3%) receiving ERBITUX during clinical studies, resulting in death in less than 1 in 1000 patients.
  - Symptoms can include trouble with breathing (including tightening of the airways, wheezing, or hoarseness), low blood pressure, shock, loss of consciousness, and/or heart attack. Report these signs and symptoms of infusion reactions, as well as fever, chills, or breathing problems to your doctor or nurse.
  - Approximately 90% of the severe allergic reactions occurred with the first dose of ERBITUX, although some patients experienced their first severe allergic reaction during a subsequent dose of ERBITUX.
  - Your doctor or nurse should watch you closely for these symptoms during treatment and may need to stop therapy in the event of an allergic reaction.
  - Severe allergic reactions require that treatment with ERBITUX be stopped immediately and not started again.

Heart Attack
- Heart attack and/or sudden death occurred in 4 of 208 patients (2%) with head and neck cancer treated with radiation therapy and ERBITUX, as compared to none of 212 patients treated with radiation therapy alone.
- Heart problems resulting in death and/or sudden death occurred in 7 of 219 patients (3%) with head and neck cancer treated with platinum-based chemotherapy with 5-fluorouracil and cetuximab compared to 4 of 215 patients (2%) treated with chemotherapy alone, based on a study conducted in Europe using European cetuximab.
- Notify your doctor if you have a history of any heart disease.

Please see Important Safety Information, including Boxed Warnings regarding allergic reactions and heart attack, on pages 18-20 and full Prescribing Information included at the end of this brochure.
This brochure, along with advice from your doctor, will help guide you and your loved ones through your treatment journey. Inside, you will find ways to:

- Learn about your diagnosis
- Understand your treatment better
- Learn about financial assistance options through Lilly PatientOne
- Care for certain side effects associated with ERBITUX treatment
- Learn about a complimentary self-care kit with information and products that may help with skin care

4 What is head and neck cancer?
6 What happens after diagnosis?
8 How was ERBITUX shown to work?
9 How will I be given ERBITUX?
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18 Important Safety Information
21 Glossary of common terms

This brochure can’t replace information or advice given by your doctor or nurse. Your healthcare team will tell you more about your condition and treatment plan and answer any questions you may have.
Metastatic cancer
Cancer that has spread from the place where it started to other places in the body. No matter where a cancer may spread, it’s always named for the place where it started. For example, head and neck cancer that has spread to the lung is called metastatic head and neck cancer, not lung cancer. Head and neck cancer most commonly spreads to the lung, followed by bone and liver.

Stages of head and neck cancer

Locally or regionally advanced cancer
Cancer that has spread from where it started to nearby tissue or lymph nodes.

Recurrent cancer
Cancer that has come back, usually after a period of time during which the cancer could not be detected.

SELECT IMPORTANT SAFETY INFORMATION

Lung Disease
- Lung disease, which resulted in one death, occurred in 4 of 1570 patients (<0.5%) receiving ERBITUX in several clinical trials in colorectal cancer and head and neck cancer.
  - Notify your doctor if you develop shortness of breath while receiving ERBITUX.
  - ERBITUX treatment should be stopped if symptoms worsen or lung disease is confirmed.

Please see Important Safety Information, including Boxed Warnings regarding allergic reactions and heart attack, on pages 18-20 and full Prescribing Information included at the end of this brochure.
What happens after diagnosis?

After your diagnosis, you and your doctor will work together to decide what the best treatment is for you. This decision will be based on a number of factors, including the size and location of the tumor, whether the tumor has spread to other areas of the body, and your general health and preferences.

Some Common treatment options for head and neck cancer

**Surgery**
A procedure or operation to remove or repair a part of the body or to find out whether disease is present.

**Radiation therapy (also called radiotherapy)**
Treatment of disease using high-energy waves or streams of particles called radiation.

**Chemotherapy**
A certain group of drugs used to treat patients with cancer.

**Biologic therapy**
A substance that is made from a living organism or its products used in the prevention, diagnosis, or treatment of cancer and other diseases. Biologic agents include antibodies, interleukins, and vaccines.

In some cases, treatments may be combined.

Assessing treatment with your healthcare team

Typically, 6-8 weeks after you start treatment, your doctor may do a CT, PET, or other kind of scan to see whether or not the treatment is working. A scan after treatment enables your doctor to tell you if your tumor disappeared, shrank, stayed the same, or grew. You may continue to have scans taken during and after treatment.

Your healthcare team

The treatment of head and neck cancer will differ from patient to patient, but it often requires the use of a team of doctors and specialists. Your healthcare team may include:

- Dentist
- Radiologist
- Medical Oncologist
- Radiation Oncologist
- Oncology Nurse
- Oral Surgeon
- Patient

Other specialists you may see during your treatment

- Dietitian
- Oral pathologist
- Prosthodontist
- Plastic surgeon
- Head and neck surgeon
- Ear, nose, and throat doctor
- Physical therapist
- Speech pathologist

Please see Important Safety Information, including Boxed Warnings regarding allergic reactions and heart attack, on pages 18-20 and full Prescribing Information included at the end of this brochure.
How was ERBITUX shown to work?

In laboratory studies, ERBITUX was shown to:

- **Block the signal**
  - ERBITUX can block one of the signals that tells a tumor cell to grow by attaching to a structure on the cell called the epidermal growth factor receptor (EGFR). This structure is found on both normal cells and tumor cells.

- **Trigger an immune response**
  - ERBITUX can form a bridge between a tumor cell and an immune cell when it is attached to the EGFR on the tumor cell. As a result, the immune cell can begin a response against the tumor cell.

EGFR

- EGFR is a receptor that is important for cell growth
- EGFR is present on some cancer cells, including head and neck cancer
- EGFR is also present on normal cells like skin, nail, or hair follicles

Laboratory studies have shown that ERBITUX does not have an effect against tumor samples that do not have EGFR.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

How will I be given ERBITUX?

- **Intravenous (IV) infusion**
  - A type of injection in which a medicine is given over time directly into the blood through a vein.

- ERBITUX is given by slow injection, also called an infusion, into a vein.

- ERBITUX is usually given once a week. Your doctor will decide how many weeks of treatment you will receive. The first dose of ERBITUX takes approximately 2 hours to give. Later doses take about 1 hour.
  - Before you begin treatment with ERBITUX, you may receive medication to help prevent an allergic reaction.

- **If you experience a side effect, your ERBITUX treatment may need to be changed, delayed, or stopped completely.**

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**WARNING: ALLERGIC REACTIONS**

**Allergic Reactions**

- **Severe allergic reactions due to ERBITUX® (cetuximab) therapy have occurred in 42 of 1373 patients (3%) receiving ERBITUX during clinical studies, resulting in death in less than 1 in 1000 patients**
  - Symptoms can include trouble with breathing (including tightening of the airways, wheezing, or hoarseness), low blood pressure, shock, loss of consciousness, and/or heart attack. Report these signs and symptoms of infusion reactions, as well as fever, chills, or breathing problems to your doctor or nurse.
  - Approximately 90% of the severe allergic reactions occurred with the first dose of ERBITUX, although some patients experienced their first severe allergic reaction during a subsequent dose of ERBITUX.
  - Your doctor or nurse should watch you closely for these symptoms during treatment and may need to stop therapy in the event of an allergic reaction.
  - Severe allergic reactions require that treatment with ERBITUX be stopped immediately and not started again.
ERBITUX may cause side effects. Some can be serious and sometimes fatal, so it is very important that you notify your doctor immediately if you develop any symptoms while receiving ERBITUX. If you experience a side effect, your ERBITUX treatment may need to be changed, delayed, or stopped completely.

Select side effects

**Allergic reactions**
Severe allergic reactions are a serious side effect with ERBITUX. Allergic reactions are rare but may cause death. Tell your doctor or nurse right away if you have trouble breathing, are wheezing or hoarse, or have fever, chills, or a tight feeling in your airways. Symptoms can also include low blood pressure, shock, loss of consciousness, and/or heart attack. Severe allergic reactions can happen at any time during treatment, but they happen most often at the first dose.

**Heart attack**
Heart attack is a serious side effect with ERBITUX. Heart attack and/or sudden death has occurred in some people who received ERBITUX and radiation therapy or cetuximab with platinum-based chemotherapy with 5-fluorouracil. Tell your doctor if you have a history of heart disease.

**Skin problems**
Skin problems are one of the most serious side effects of ERBITUX. Skin problems include an acne-like rash, skin drying and cracking, infections, and abnormal hair growth. The skin around your fingernails and toenails may swell. Blistering of the skin or mucous membranes (such as the mouth) or peeling of the skin may be symptoms of serious reactions that could lead to death. Contact your doctor right away if you have any of these symptoms.

ERBITUX may cause an acne-like skin rash.
An acne-like skin rash during EGFR treatment may:

- Look like acne, but it is not
- Be red, swollen, crusty, and very dry
- Feel itchy, tender, painful, or warm or burning (like a sunburn)
- Happen on the scalp, face, chest, or upper back, or other parts of the body if the case is severe
- Start and may be worse during the first few weeks of treatment
- Get better or stay the same during treatment
- Go away after treatment is stopped, but not always immediately
- Become infected
- Cause the skin to change color after the rash has gone away

ERBITUX may cause nail changes.
Nail changes during EGFR treatment may:

- Look like pus-filled blisters or swollen, red skin around the fingernails or toenails
- Cause ingrown nails or infection
- Cause nails to form ridges or to fall off
- Be swollen and painful
- Appear 2 to 4 months after starting treatment
- Last for many months after treatment

ERBITUX may cause hair changes.
Hair changes during EGFR treatment may:

- Make the eyelashes grow very fast and become very long and bother your eyes
- Cause fast growth to eyebrows
- Cause hair on the scalp to become curly, fine, or brittle
- Start a few weeks to months after starting treatment and go away after treatment is stopped

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Side effects for each person may vary. Tell your doctor or nurse if you notice any skin, nail, or hair changes, or any other side effects.

Platinum agents
Anticancer medicines that are made from the metal platinum.

5-fluorouracil
A drug used to treat certain cancers. Also called 5-FU.

For more definitions, please see page 21.
Participate in your treatment. Talk to your healthcare provider about your side effects.

**Tips to help care for skin problems**
- Talk to your doctor or nurse about management of skin problems
- Your doctor or nurse may suggest the use of moisturizing lotion to help keep skin moist
- They may also suggest cool compresses to relieve itching
- Being out in the sun may make skin problems worse. People receiving ERBITUX should wear sunscreen and hats and limit sun exposure during treatment and for 2 months following the last dose of ERBITUX
- Rash may be treated with antibiotics. Antibiotics may be in pill form (and may be taken by mouth) or as a skin cream

**Tips to help care for diarrhea**
- Tell your doctor if you experience diarrhea
- Eat many small meals, rather than 3 normal-size meals
- Eat Bananas, white Rice, Applesauce, white Toast (the BRAT diet)
- Drink plenty of water, clear liquids, or sports drinks

**Tips to help care for fatigue and/or weakness**
- Tell your doctor if you have fatigue or weakness
- Make a plan for each day that includes time for activity and time for rest. Try to do the most important things first, while you have energy
- Keep a journal of how you feel each day, noting when you are tired or feeling energetic
- Do small amounts of activity to give yourself energy
- For persistent fatigue, talk to your doctor

**Tips to help care for nausea**
- Tell your doctor if you have nausea
- Eat smaller meals more often during the day
- Eat foods that are light or bland (have a mild flavor), such as chicken noodle soup or scrambled eggs
- Eat dry foods, such as crackers, bread, or dry cereal, when you first wake up or if your stomach is empty
- Sip clear liquids, such as water or a sports drink, or suck on ice chips or ice pops
- Rest a bit after eating, but avoid lying down flat for at least 1 hour after a meal
- Rinse your mouth before and after you eat a meal

You may experience other side effects while being treated with ERBITUX. Your treatment team is there to help, so be sure to let them know about any side effects that are bothering you.

Please see Important Safety Information, including Boxed Warnings regarding allergic reactions and heart attack, on pages 18-20 and full Prescribing Information included at the end of this brochure.
Caring for your skin, nails, and hair during treatment

Get your complimentary self-care kit
The self-care kit contains information on the possible side effects of EGFR inhibitors, such as ERBITUX, as well as products and suggestions to help with skin care. Using the tips and materials in the self-care kit may help manage side effects. If you have any questions, please be sure to discuss them with your treatment team. Talk to your doctor to determine if the self-care kit is right for you.

The self-care kit includes

Advice
- A brochure with information about potential skin, nail, and hair changes
- Helpful tips

Care products
- Lotions
- Sunscreen
- Gentle bathing products
- Nail care kit

Ask your doctor or visit ERBITUX.com for more information about the self-care kit.

PatientOne

Lilly PatientOne may help with the costs of your prescribed Lilly Oncology medications

Find easy-to-use forms and reimbursement information to help support your patient’s treatment journey.

Lilly PatientOne is committed to helping eligible patients access support programs for Lilly Oncology products they are prescribed. We aim to address both financial and coverage issues for qualified uninsured, underinsured, and insured patients. Lilly PatientOne strives to offer resources, ranging from benefits investigations to financial assistance and appeals information, that provide reliable and individualized treatment support for eligible patients.

For more information about Lilly PatientOne, call 1-866-4PatOne (1-866-472-8663), Monday–Friday, 9 AM–7 PM ET, or visit LillyPatientOne.com.
What does it mean to be a caregiver?

After cancer is diagnosed, the person you love will face a challenging journey. As a caregiver, you will share that journey and become a source of comfort and support. As a caregiver, you are going to help your loved one with everyday tasks. These can include:
- Preparing food
- Helping with things around the house
- Taking them to the doctor

Your most important role as a caregiver is providing emotional and spiritual support for your loved one. It is also important to be there to help them cope with their cancer and provide support through their treatment.

As a caregiver, it’s important to take care of yourself, too

While caring for your loved one, you may feel as if you don’t have time to take care of yourself. After a while your emotional and physical well-being may suffer. Taking care of yourself will help you take better care of your loved one. Make time for yourself every day.

10 ways to help care for yourself
- Find comfort in things you enjoy doing
- Look for positives to bring your spirits up
- Find acceptance and vow to live each day to its fullest
- Feel thankful that you can be there for your loved one
- Connect with other people so you won’t get overwhelmed
- Let yourself laugh to release tension
- Write in a journal to relieve negative thoughts
- Confront your anger and try to defuse it the moment it happens
- Let go of your guilt to help you focus on what you need to do
- Join a support group so you know you’re not alone

Tips to help maintain your health
- Eating well will help you keep up your strength
- Get plenty of rest to stay energized during the day
- Exercise is a great way to keep your body healthy and mind clear
- Learn how to relax to help relieve stress

You can get support

You’re not alone, but sometimes when looking after your loved one it may feel that way. This can cause increased levels of stress, feelings of being overwhelmed, and even physical sickness. Remember, there is nothing wrong with asking for help.

To find support, contact:
Caregiver Action Network
1-301-942-6430
www.caregiveraction.org

If the responsibility of caring for your loved one is causing you to experience signs of fatigue, weight loss or weight gain, changes in appetite, headaches, or mood swings, be sure to speak with your physician.
IMPORTANT SAFETY INFORMATION

WARNING: ALLERGIC REACTIONS and HEART ATTACK

Allergic Reactions
- Severe allergic reactions due to ERBITUX® (cetuximab) therapy have occurred in 42 of 1373 patients (3%) receiving ERBITUX during clinical studies, resulting in death in less than 1 in 1000 patients
  - Symptoms can include trouble with breathing (including tightening of the airways, wheezing, or hoarseness), low blood pressure, shock, loss of consciousness, and/or heart attack. Report these signs and symptoms of infusion reactions, as well as fever, chills, or breathing problems to your doctor or nurse
  - Approximately 90% of the severe allergic reactions occurred with the first dose of ERBITUX, although some patients experienced their first severe allergic reaction during a subsequent dose of ERBITUX
  - Your doctor or nurse should watch you closely for these symptoms during treatment and may need to stop therapy in the event of an allergic reaction
  - Severe allergic reactions require that treatment with ERBITUX be stopped immediately and not started again

Heart Attack
- Heart attack and/or sudden death occurred in 4 of 208 patients (2%) with head and neck cancer treated with radiation therapy and ERBITUX, as compared to none of 212 patients treated with radiation therapy alone
- Heart problems resulting in death and/or sudden death occurred in 7 of 219 patients (3%) with head and neck cancer treated with platinum-based chemotherapy with 5-fluorouracil and cetuximab compared to 4 of 215 patients (2%) treated with chemotherapy alone, based on a study conducted in Europe using European cetuximab
- Notify your doctor if you have a history of any heart disease

Skin Problems
- In several clinical studies in colorectal cancer and head and neck cancer with ERBITUX, skin problems including an acne-like rash, skin drying and cracking, infections (including infections of the blood, skin, eyes, and lips), and abnormal hair growth were seen
  - Sun exposure may worsen these effects
  - Patients taking ERBITUX should wear sunscreen and hats to limit sun exposure while receiving and for 2 months following the last dose of ERBITUX
  - Severe reactions with symptoms of rash; blistering of the skin, mouth, eyes, and genitals; and shedding of the skin have been seen in patients treated with ERBITUX. These reactions may be life-threatening and possibly lead to death. It is not clear if these reactions are related to the way ERBITUX works or to an immune response, such as Stevens-Johnson syndrome or toxic epidermal necrolysis
  - A related nail disorder that causes painful swelling of the skin around the nails—most often of the large toes and thumbs—also was reported
  - Notify your doctor if you develop any of these symptoms while receiving ERBITUX

Lung Disease
- Lung disease, which resulted in one death, occurred in 4 of 1570 patients (<0.5%) receiving ERBITUX in several clinical trials in colorectal cancer and head and neck cancer
  - Notify your doctor if you develop shortness of breath while receiving ERBITUX
  - ERBITUX treatment should be stopped if symptoms worsen or lung disease is confirmed

Erbitux Plus Chemotherapy and Radiation
- In a controlled study, 940 patients with head and neck cancer received either ERBITUX with radiation therapy and cisplatin (a cancer drug) or radiation therapy and cisplatin alone. Adding ERBITUX resulted in an increase in occurrence of severe or life-threatening redness and sores of the lining of the mouth, lips or throat and other digestive organs; skin reactions caused by certain cancer drugs given after radiation; acne-like rash; heart problems and blood electrolyte disturbances compared to radiation and cisplatin alone
  - Side effects resulting in death occurred in 20 patients (4.4%) in the ERBITUX treatment arm, and 14 patients (3.0%) in the radiation therapy and cisplatin alone treatment arm
  - Nine patients in the ERBITUX treatment arm (2.0%) experienced decreased blood flow to the heart compared to 4 patients (0.9%) in the radiation therapy and cisplatin alone treatment arm
  - The main point of the study was to measure how long patients survived before their cancer got worse. Adding ERBITUX to radiation and cisplatin did not improve this measure

Electrolyte Depletion
- Low levels of magnesium and accompanying low calcium and potassium levels have been reported with ERBITUX when given by itself and in combination with other cancer drugs
  - Your doctor or nurse should periodically monitor your blood electrolyte levels and administer intravenous replacement as needed

Late Radiation Side Effects
- The percentage of late radiation side effects was higher in patients given ERBITUX with radiation therapy compared with patients given radiation therapy alone
  - The following sites were affected: organs that produce saliva (65%/56%), voice box (52%/36%), tissue below the skin (49%/45%), lining of the mouth and some organs (48%/39%), food pipe (44%/35%), and skin (42%/33%) in the patients given ERBITUX and radiation versus patients given radiation alone, respectively
  - The percentage of severe late radiation side effects was similar among patients given radiation therapy alone and patients given ERBITUX plus radiation therapy

Pregnancy and Nursing
- Notify your doctor if you are pregnant or if you become pregnant while receiving ERBITUX. Contraception must be used, in both males and females, during ERBITUX therapy and for 6 months following the last dose of ERBITUX. ERBITUX may be passed from the mother to the developing fetus, and may cause harm to the fetus. ERBITUX should only be used during pregnancy if the potential benefit is greater than the potential risk to the fetus
  - ERBITUX may be passed through human breast milk. Because of the potential for serious side effects in nursing infants from ERBITUX, nursing is not recommended during ERBITUX therapy and for 2 months following the last dose of ERBITUX

Please see Important Safety Information continued on the next page and full Prescribing Information for ERBITUX, including Boxed Warnings regarding allergic reactions and heart attack, included at the end of this brochure.
IMPORTANT SAFETY INFORMATION (CONTINUED)

Additional Side Effects

In studies of ERBITUX:

- The most serious side effects associated with ERBITUX across all clinical studies are: allergic reactions, heart attack, skin problems, skin irritation in the radiation area, infection, kidney failure, lung disease, and blood clots in the lung.

- The most frequent side effects associated with ERBITUX (reported in at least 25% of patients) are skin problems (including rash, itching, and nail changes), headache, diarrhea, and infection.

In a study of ERBITUX and radiation therapy given to 208 patients versus radiation therapy alone given to 212 patients with head and neck cancer:

- The most frequent side effects were: acne-like rash (87% versus 10%), skin irritation in the radiation area (86% versus 90%), weight loss (84% versus 72%), and feeling weak (56% versus 49%).

- Serious side effects reported by at least 10% of patients that received ERBITUX in combination with radiation therapy versus radiation therapy alone included: skin irritation in the radiation area (23% versus 16%), acne-like rash (17% versus 1%), and weight loss (11% versus 7%).

In a study of European cetuximab in combination with platinum-based chemotherapy with 5-fluorouracil given to 219 patients versus chemotherapy alone given to 215 patients with head and neck cancer:

- The most frequent side effects were: acne-like rash (70% versus 2%), nausea (54% versus 47%), and infection (44% versus 27%).

- Serious side effects reported by at least 10% of patients in either arm were: infection (11% versus 8%).

- ERBITUX yields approximately 22% higher blood levels of cetuximab relative to European cetuximab. It is possible that U.S. patients receiving ERBITUX may experience more frequent or severe side effects than patients in the study conducted in Europe.

You are encouraged to report negative side effects of Prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see full Prescribing Information for ERBITUX, including Boxed Warnings for allergic reactions and heart attack, included at the end of this brochure.

Glossary of common terms

5-fluorouracil: A drug used to treat certain cancers. Also called 5-FU.

Allergic reaction: A reaction that happens when a person comes in contact with a substance to which that person is especially sensitive.

Cell: The individual unit that makes up the tissues of the body.

Computed tomography (CT) scan: Also called a CAT scan, which is a series of detailed pictures of areas inside the body created by a computer linked to an X-ray machine.

Diagnosis: The process of identifying a disease, such as cancer, from its signs and symptoms. A health history, physical exam, and tests may be used to make a diagnosis.

EGFR: EGFR is a receptor found on both normal and tumor cells that is important for cell growth.

Intravenous (IV) infusion: A type of injection in which a medicine is given over time directly into the blood through a vein.

Lymph node: Lymph nodes filter lymph (lymphatic fluid), and they store lymphocytes (white blood cells).

Metastatic: The cancer has spread from the place where it started to other places in the body.

Platinum agents: Anticancer medicines that are made from the metal platinum.

Positron emission tomography (PET) scan: A procedure in which a small amount of radioactive sugar is injected into a vein, and a scanner is used to make pictures of areas inside the body where the sugar is taken up. Cancer cells often take up more sugar than normal cells, so a PET scan can be used to find cancer cells in the body.

Scan: A picture of structures inside the body. Scans often used in diagnosing, staging, and monitoring disease include liver scans, bone scans, computed tomography (CT) or computerized axial tomography (CAT) scans, and magnetic resonance imaging (MRI) scans.

Side effect: A problem that occurs when treatment affects healthy tissues or organs.

Squamous cell carcinoma: Cancer that begins in thin, flat cells that make up the lining of many areas of the body, including many parts of the head and neck.

Tumor: An abnormal mass of tissue that forms when cells grow and divide uncontrollably. A tumor may be either benign (not cancerous) or malignant (cancerous).
Get involved: Educate yourself.

Educating yourself—whether it’s your diagnosis or a loved one’s—is an important step, regardless of whether you’re newly diagnosed or have been living with head and neck cancer for a while. There are many outside resources you can turn to, whether you want to learn more about your cancer or you’re looking for support from other people who are going through the same thing.

Websites you may find helpful

**SUPPORT**
Association of Cancer Online Resources®
1-212-226-5525 • www.acor.org

CancerCare®
1-800-813-HOPE (1-800-813-4673)
www.cancercare.org

Cancer Information Service
1-800-4-CANCER (1-800-422-6237)
www.cancer.gov/aboutnci/cis

Cancer Support Community
1-888-793-9355
www.cancersupportcommunity.org

LIVESTRONG
1-855-220-7777 • www.livestrong.org

**EDUCATION**
American Cancer Society®
1-800-ACS-2345 (1-800-227-2345)
www.cancer.org

National Cancer Institute
1-800-4-CANCER (1-800-422-6237)
www.cancer.gov

National Comprehensive Cancer Network®
1-215-690-0300 • www.nccn.org/patients/

Prevent Cancer Foundation
1-800-227-2732 • www.preventcancer.org

**ADVOCACY**
National Coalition for Cancer Survivorship
1-877-NCCS-YES (1-877-622-7937)
www.canceradvocacy.org

Patient Advocate Foundation
1-800-532-5274 • www.patientadvocate.org

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**INDICATIONS AND USAGE**

Erbxit® 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 5-FU. (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 FDA-approved tests
    - 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)

Limitation of Use: Erbitux is not indicated for treatment of Ras-mutant colorectal cancer. (5.7, 14.2)

**DOSE AND ADMINISTRATION**

- Premedicate with an H3 antagonist. (2.3)
- Administer 400 mg/m2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m2 weekly infused over 60 minutes. (2.1, 2.2)
- Initiate Erbitux one week prior to initiation of radiation therapy. Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU (2.1) and FOLFI (2.2).
- Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 infusion reactions and non-serious NCI CTC Grade 3 infusion reaction. (2.4)
- Permanently discontinue for serious infusion reactions. (2.4)
- Withhold infusion for severe, persistent acneiform rash. Reduce dose for recurrent, severe rash. (2.4)

**ADVERSE REACTIONS**

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

To report SUSPECTED ADVERSE REACTIONS, contact 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**

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2016
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. [See Clinical Studies (14.1)].

Erbitux is indicated in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck. [See Clinical Studies (14.1)].

Erbitux, as a single agent, is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. [See Clinical Studies (14.1)].

1.2 K-Ras Wild-type, EGFR-expressing Colorectal Cancer

Erbitux is indicated for the treatment of K-Ras wild-type, epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use [see Dosage and Administration (2.2), Warnings and Precautions (5.7), Clinical Studies (14.2)].

- in combination with FOLFI RI (irinotecan, 5-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. [See Warnings and Precautions (5.7), Clinical Pharmacology (12.1), Clinical Studies (14.2)].

Limitation 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), Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Squamous Cell Carcinoma of the Head and Neck

Erbitux in combination with radiation therapy or in combination with platinum-based therapy with 5-FU:
- The recommended initial dose is 400 mg/m² administered one week prior to initiation of a course of radiation therapy or on the day of initiation of platinum-based therapy with 5-FU as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min). Complete Erbitux administration 1 hour prior to platinum-based therapy with 5-FU.
- The recommended subsequent weekly dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) for the duration of radiation therapy (6–7 weeks) or until disease progression or unacceptable toxicity when administered in combination with platinum-based therapy with 5-FU. Complete Erbitux administration 1 hour prior to radiation therapy or platinum-based therapy with 5-FU.

Erbitux monotherapy:
- The recommended initial dose is 400 mg/m² administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min).
- The recommended subsequent weekly dose (all other infusions) is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity.

2.2 Colorectal Cancer

- 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 colorectal cancer is available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/ invitrodiagnostics/ucm501431.htm.
- The recommended initial dose, either as monotherapy or in combination with irinotecan or FOLFIRI (irinotecan, 5-fluorouracil, leucovorin), is 400 mg/m² administered as a 120-minute intravenous infusion (maximum infusion rate 10 mg/min). Complete Erbitux administration 1 hour prior to FOLFIRI.
- The recommended subsequent weekly dose, either as monotherapy or in combination with irinotecan or FOLFIRI, is 250 mg/m² infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity. Complete Erbitux administration 1 hour prior to FOLFIRI.

2.3 Recommended Premedication

Premedicate with an H₂ antagonist (eg, 50 mg of diphenhydramine) intravenously 30–60 minutes prior to the first dose; premedication should be administered for subsequent Erbitux doses based upon clinical judgment and presence/severity of prior infusion reactions.

2.4 Dose Modifications

Infusion Reactions

Reduce the infusion rate by 50% for NC1 CTC Grade 1 or 2 and non-serious NC1 CTC Grade 3 infusion reaction. Immediately and permanently discontinue Erbitux for serious infusion reactions, requiring medical intervention and/or hospitalization. [See Warnings and Precautions (5.1)].

Dermatologic Toxicity

Recommended dose modifications for severe (NC1 CTC Grade 3 or 4) acneiform rash are specified in Table 1. [See Warnings and Precautions (5.4)].

Table 1: Erbitux Dose Modification Guidelines for Rash

<table>
<thead>
<tr>
<th>Severe Acneiform Rash</th>
<th>Erbitux</th>
<th>Outcome</th>
<th>Erbitux Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence Delay infusion 1 to 2 weeks Improvement No Improvement Continue at 250 mg/m² Discontinue Erbitux</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd occurrence Delay infusion 1 to 2 weeks Improvement No Improvement Reduce dose to 200 mg/m² Discontinue Erbitux</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd occurrence Delay infusion 1 to 2 weeks Improvement No Improvement Reduce dose to 150 mg/m² Discontinue Erbitux</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th occurrence Discontinue Erbitux</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.5 Preparation for Administration

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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. 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.

3 DOSAGE FORMS AND STRENGTHS

100 mg/50 mL, single-use vial
200 mg/100 mL, single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of Erbitux included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NC1 CTC Grades 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in Studies 1, 3, 5, and 6 receiving Erbitux, with fatal outcome in 1 patient. [See Clinical Studies (14.1, 14.2)].

- Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.
- Monitor patients for 1 hour following Erbitux infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.
- Immediately and permanently discontinue Erbitux in patients with serious infusion reactions. [See Boxed Warning, Dosage and Administration (2.4)].

5.2 Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and Erbitux as compared to none of 212 patients treated with radiation therapy alone in Study 1. 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 Study 2, fatal cardiac disorders and/or sudden death occurred in 7 (3%) of 219 patients treated with EU-approved cetuximab and platinum-based therapy with 5-FU as compared to 4 (2%) of 215 patients treated with chemotherapy alone. Five of these 7 patients in the chemotherapy plus cetuximab arm received concomitant cisplatin and 2 patients received concomitant carboplatin. All 4 patients in the chemotherapy-alone arm received cisplatin. Carefully consider use of Erbitux in combination with radiation therapy or platinum-based therapy with 5-FU in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after Erbitux. [See Boxed Warning, Warnings and Precautions (5.6)].
5.3 Pulmonary Toxicity
Intestinal lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving Erbitux in Studies 1, 3, and 6, as well as other studies, in colorectal cancer and head and neck cancer. Interrupt Erbitux for acute onset or worsening of pulmonary symptoms. Permanently discontinue Erbitux for confirmed ILD.

5.4 Dermatologic Toxicity
Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving Erbitux therapy. Acneiform rash occurred in 76–88% of 1373 patients receiving Erbitux in Studies 1, 3, 5, and 6. Severe acneiform rash occurred in 1–17% of patients.

Acneiform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Erbitux. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, 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. [See Dosage and Administration (2.4).]

5.5 Use of Erbitux 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 and cisplatin alone. The addition of Erbitux resulted in an increase in the incidence of Grade 3–4 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 20 patients (4.4%) in the Erbitux combination arm and 14 patients (3.0%) in the control arm. Nine patients in the Erbitux arm (2.0%) experienced noncardiac myocardial ischemia compared to 4 patients (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.

5.6 Hypomagnesemia and Electrolyte Abnormalities
In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of 365 patients receiving Erbitux in Study 5 and two other clinical trials in colorectal cancer and head and neck cancer, respectively, and was severe (NCI CTC Grades 3 and 4) in 6–17%.

In Study 2, where EU-approved cetuximab was administered in combination with platinum-based therapy, the addition of cetuximab to cisplatin and 5-FU resulted in an increased incidence of hypomagnesemia (14% vs. 6%) and of Grade 3–4 hypomagnesemia (7% vs. 2%) compared to cisplatin and 5-FU alone. In contrast, the incidences of hypomagnesemia were similar for those who received cetuximab, carboplatin, and 5-FU compared to carboplatin and 5-FU (4% vs. 4%). No patient experienced Grade 3–4 hypomagnesemia in either arm in the carboplatin subgroup.

The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of Erbitux. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia. 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. The most serious adverse reactions with Erbitux are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

Across Studies 1, 3, 5, and 6, Erbitux was discontinued in 3–10% of patients because of adverse reactions.

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 below reflect exposure to Erbitux in 1373 patients with SCCHN or colorectal cancer in randomized Phase 3 (Studies 1 and 5) or Phase 2 (Studies 3 and 6) trials treated at the recommended dose and schedule for medians of 7 to 14 weeks. [See Clinical Studies (14)].

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.

Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

Renal: Renal failure occurred in 1% of patients with colorectal cancer.

Squamous Cell Carcinoma of the Head and Neck

Erbitux in Combination with Radiation Therapy
Table 2 contains selected adverse reactions in 420 patients receiving radiation therapy either alone or with Erbitux for locally or regionally advanced SCCHN in Study 1. Erbitux was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 8 infusions (range 1–11).

Table 2: Incidence of Selected Adverse Reactions (≥10%) in Patients with Locoregionally Advanced SCCHN

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>Grades 1–4</th>
<th>Grades 3 and 4</th>
<th>Grades 1–4</th>
<th>Grades 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Athetosis</td>
<td>56</td>
<td>4</td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Fevera</td>
<td>29</td>
<td>1</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>19</td>
<td>&lt;1</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>Infusion Reactionb</td>
<td>15</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>13</td>
<td>1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Chilsc</td>
<td>16</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Digestive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>49</td>
<td>2</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Emesis</td>
<td>29</td>
<td>2</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>19</td>
<td>2</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>14</td>
<td>0</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Metabolic/Nutritional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight Loss</td>
<td>84</td>
<td>11</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>25</td>
<td>6</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Alatine Transaminase, highd</td>
<td>43</td>
<td>2</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Aspartate Transaminase, highd</td>
<td>38</td>
<td>1</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Alkaline Phosphatase, highd</td>
<td>33</td>
<td>&lt;1</td>
<td>24</td>
<td>0</td>
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<tr>
<td></td>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td>26</td>
<td>3</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Skin/Appendages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acneiform Rasha</td>
<td>87</td>
<td>17</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Radiation Dermatitis</td>
<td>86</td>
<td>23</td>
<td>90</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Application Site Reaction</td>
<td>18</td>
<td>0</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>16</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

a Includes cases also reported as infusion reaction.

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

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

d Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “purpural rash”, “dry skin”, or “exfoliative dermatitis”.

The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both arms of the study.

ERBITUX® (cetuximab) injection, for intravenous infusion

ERBITUX® (cetuximab) injection, for intravenous infusion
Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in 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 plus radiation treatment groups.

Study 2: EU-Applied Cetuximab in Combination with Platinum-based Therapy with 5-Fluorouracil

Study 2 used EU-approved cetuximab. Since U.S.-licensed Erbitux provides approximately 22% higher exposure relative to the EU-approved cetuximab, 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)].

Table 3 contains selected adverse reactions in 434 patients with recurrent locoregional disease or metastatic SCCCHN receiving EU-approved cetuximab in combination with platinum-based therapy with 5-FU or platinum-based therapy with 5-FU alone in Study 2. Cetuximab was administered at 400 mg/m² for the initial dose, followed by 250 mg/m² weekly. Patients received a median of 17 infusions (range 1–89).

Table 4 contains selected adverse reactions in 667 patients with K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer receiving EU-approved cetuximab plus FOLFIRI or FOLFIRI alone in Study 4 (see Warnings and Precautions (5.8)). Cetuximab was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 26 infusions (range 1–224).

Table: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with K-Ras Wild-type and EGFR-expressing, Metastatic Colorectal Cancer

**Table 3:** Incidence of Selected Adverse Reactions (≥10%) in Patients with Recurrent Locoregional Disease or Metastatic SCCHN

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>EU-Applied Cetuximab plus Platinum-based Therapy with 5-FU (n=219)</th>
<th>Platinum-based Therapy with 5-FU Alone (n=215)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4</td>
<td>Grades 3 and 4</td>
<td>Grades 1–4</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>10.0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>54.0%</td>
<td>4.0%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26.0%</td>
<td>5.0%</td>
<td>16.1%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Pyrexia</td>
<td>22.0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Infusion Reaction</td>
<td>10.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Infection</td>
<td>44.0%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Anorexia</td>
<td>25.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia</td>
<td>12.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>12.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia</td>
<td>11.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Acneiform Rash</td>
<td>70.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>28.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td>22.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>Dermatitis Acneiform</td>
<td>15.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td></td>
<td>Dry Skin</td>
<td>14.0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
<td>12.0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 4:** Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with K-Ras Wild-type and EGFR-expressing, Metastatic Colorectal Cancer

**Table 5:** Incidence of Selected Adverse Reactions in 242 Patients with K-Ras Abnormal, EGFR-expressing, Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grades 1–4</th>
<th>Grades 3 and 4</th>
<th>Grades 1–4</th>
<th>Grades 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Neutropenia</td>
<td>49.0%</td>
<td>31.0%</td>
<td>42.0%</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Conjunctivitis</td>
<td>18.0%</td>
<td>&lt;1.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhea</td>
<td>66.0%</td>
<td>16.0%</td>
<td>60.0%</td>
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<tr>
<td></td>
<td>Stomatitis</td>
<td>31.0%</td>
<td>3.0%</td>
<td>19.0%</td>
</tr>
<tr>
<td></td>
<td>Dysepsis</td>
<td>16.0%</td>
<td>0.0%</td>
<td>9.0%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>General Reaction</td>
<td>14.0%</td>
<td>2.0%</td>
<td>&lt;1.0%</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>26.0%</td>
<td>1.0%</td>
<td>14.0%</td>
</tr>
<tr>
<td></td>
<td>Infections and Infestations</td>
<td>Paronychia</td>
<td>20.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Investigations</td>
<td>Weight Decreased</td>
<td>15.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>Metabolism and Nutrition Disorders</td>
<td>Anorexia</td>
<td>30.0%</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Acne-like Rash</td>
<td>86.0%</td>
<td>18.0%</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td>44.0%</td>
<td>9.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Dermatitis Acneiform</td>
<td>26.0%</td>
<td>5.0%</td>
<td>&lt;1.0%</td>
</tr>
<tr>
<td></td>
<td>Dry Skin</td>
<td>22.0%</td>
<td>0%</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td>14.0%</td>
<td>2.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>14.0%</td>
<td>0%</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>Palmar-planter</td>
<td>Erythrodysesthesia Syndrome</td>
<td>19.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td></td>
<td>Skin Rashes</td>
<td>19.0%</td>
<td>2.0%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Adverse reactions occurring in at least 10% of Erbitux combination arm with a frequency at least 5% greater than that seen in the FOLFIRI arm.

Adverse reactions were graded using the NCI CTC, V 2.0.

Infusion related reaction is 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 using MedDRA preferred terms: "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", "hypertension", "infusion related reaction", "loss of consciousness", "myocardial infarction", "myocardial ischaemia", "pinprickwind aniga", "shock", "sudden death", "syncope", or "systolic hypertension".

Acne-like rash is defined as any event meeting the medical concepts of acneiform rash, "acne", "dermatitis acniform", "dry skin", "erythema", "exfoliative rash", "flush", "rash erythematous", "rash macular", "rash papular", or "rash pustular".
Table 5: Incidence of Selected Adverse Reactions Occurring in ≥10% of Patients with K-Ras Wild-type, EGFR-expressing, Metastatic Colon/Rectal Cancer Treated with Erbitux Monotherapy

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>Erbitux plus BSC (n=118)</th>
<th>BSC alone (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1–4</td>
<td>Grades 3 and 4</td>
<td>Grades 1–4</td>
</tr>
<tr>
<td>Dermatology/Skin</td>
<td>% of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash/Desquamation</td>
<td>95</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>57</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Pruritus</td>
<td>47</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Other-Dermatology</td>
<td>35</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Nail Changes</td>
<td>31</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Constitutional Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>91</td>
<td>31</td>
<td>79</td>
</tr>
<tr>
<td>Fever</td>
<td>25</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Infusion Reactions²</td>
<td>18</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rigors, Chills</td>
<td>16</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td>59</td>
<td>18</td>
<td>37</td>
</tr>
<tr>
<td>Headache</td>
<td>38</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>15</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>49</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>65</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>Constipation</td>
<td>53</td>
<td>3</td>
<td>38</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Other-Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>13</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Mouth Dryness</td>
<td>12</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Taste Disturbance</td>
<td>10</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>38</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>45</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>Insomnia</td>
<td>27</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Confusion</td>
<td>18</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Anxiety</td>
<td>14</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Depression</td>
<td>14</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

¹ Adverse reactions occurring in at least 10% of Erbitux plus BSC arm with a frequency at least 5% greater than that seen in the BSC alone arm.
² Adverse reactions were graded using the NCI CTC, V 2.0.
³ Infusion reaction is 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.

6.3 Postmarketing Experience

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

- Aseptic meningitis
- Mucosal inflammation
- Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, life-threatening and fatal bullous mucocutaneous disease

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Erbitux in pregnant women. Based on animal models, Erbitux has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Human IgG is known to cross the placental barrier; therefore, Erbitux may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Erbitux should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant cynomolgus monkeys were treated weekly with 0.4 to 4 times the recommended human dose of cetuximab (based on body surface area) during the period of organogenesis (gestation day [GD] 20–48). Cetuximab was detected in the amniotic fluid and in the serum of embryos from treated dams at GD 40. No fetal malformations or other teratogenic effects occurred in offspring. However, significant increases in embryolethality and abortions occurred at doses of approximately 1.6 to 4 times the recommended human dose of cetuximab (based on total body surface area).

8.3 Nursing Mothers

It is not known whether Erbitux is secreted in human milk. IgG antibodies, such as Erbitux, can be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Erbitux, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If nursing is interrupted, based on the mean half-life of cetuximab [see Clinical Pharmacology (12.3)], nursing should not be resumed earlier than 60 days following the last dose of Erbitux.

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/m², 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 pharmacokinetic profiles of cetuximab between the two age groups were similar at the 75 and 150 mg/m² single dose levels. The volume of distribution of the determination to be independent of dose and approximated the vascular space of 2–3 L/m². Following a single dose of 250 mg/m², the geometric mean AUC₀→∞ (C₀V) value 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 (range 69 to 188 hours) for the younger age group, and 82 hours (range 55 to 117 hours) for the adolescent age group.

8.5 Geriatric Use

Of the 1662 patients who received Erbitux with irinotecan, FOLFIRI or Erbitux monotherapy in six studies of advanced colorectal cancer, 588 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.

10 OVERDOSAGE

The maximum single dose of Erbitux administered is 1000 mg/m² in one patient. No adverse events were reported for this patient.

11 DESCRIPTION

Erbitux 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 is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Erbitux is supplied at a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use vials. Cetuximab is formulated in a solution with no preservatives, which contains 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

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 kinase domain is activated by binding a variety of ligands, such as epidermal growth factor (EGF), transforming growth factor α (TGF α), amphiregulin, betacellulin, epiregulin, epigen, neuregulin-1, and heregulin. Once activated, the EGFR dimer binds to the catalytic site, and autophosphorylates tyrosine residues in the cytoplasmic domain of the receptor. This allows other downstream signaling pathways to be activated. EGFR pathway mediates cellular processes such as cell proliferation, differentiation, migration, and apoptosis.

13.4 mg•h/mL (38%) in the adolescent group (13–18 years, n=6). The mean half-life of cetuximab was 110 hours (range 69 to 188 hours) for the younger age group, and 82 hours (range 55 to 117 hours) for the adolescent age group.
Effects on Electrocardiogram (ECG) compared to radiation therapy or chemotherapy alone. Tumor types.

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.

12.2 Pharmacodynamics

Effects on Electrocardiogram (EGG)

The effect of cetuximab on QT interval was evaluated in an open-label, single-arm, monotherapy trial in 37 subjects with advanced malignancies who received an initial dose of 400 mg/m², followed by weekly infusions of 250 mg/m² for a total of 5 weeks. No large changes in the mean QT interval of >20 ms from baseline were detected in the trial based on the Fridericia correction method. A small increase in the mean QTC interval of <10 ms cannot be excluded because of the limitations in the trial design.

12.3 Pharmacokinetics

Erbitux administered as monotherapy 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 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m².

Following the recommended dose regimen (400 mg/m² initial dose; 250 mg/m² 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 to 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with SCCHN and those with colorectal cancer.

Erbitux had an approximately 22% (90% confidence interval; 6%, 38%) higher systemic exposure relative to the EU-approved cetuximab. The mean half-life of cetuximab was approximately 1.5 days (range 1.0–2.5 days). The volume of distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m².

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 other evidence of genotoxic potential of cetuximab was observed in the Salmonella typhimurium and mouse micronucleus assay or in the in vitro rat micronucleus test. Mammalian cell growth was impaired in female cynomolgus monkeys receiving weekly doses of 0.4 to 4 times the human dose of cetuximab (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 week 25 of cetuximab treatment and continued through the 6-week recovery period. In this same study, there were no effects of cetuximab treatment on measured male fertility parameters (i.e., serum testosterone levels and analysis of sperm counts, viability, and motility) as compared to control male monkeys. It is not known if cetuximab can impair fertility in humans.

13.2 Animal Pharmacology and/or Toxicology

In cynomolgus monkeys, cetuximab, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epidermal muscosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the oral tubal epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 15 weeks of treatment.

14 CLINICAL STUDIES

Studies 2 and 4 were conducted outside the U.S. using an EU-approved cetuximab as the clinical trial material. Erbitux provides approximately 22% higher exposure relative to the EU-approved cetuximab used in Studies 2 and 4; these pharmacokinetic data, together with the results of Studies 2, 4, and other clinical trial data establish the efficacy of Erbitux at the recommended dose in SCCHN and mCRC [see Clinical Pharmacology (12.3)].

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

Study 1 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 plus 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 as a 400 mg/m² initial dose beginning one week prior to initiation of radiation therapy, followed by 250 mg/m² weekly administered 1 hour prior to radiation therapy for the duration of radiation therapy (6–7 weeks).

Of the 424 randomized patients, the median age was 57 years, 80% were male, 83% were Caucasian, and 90% had baseline Karnofsky performance status >80. There were 256 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. The main outcome measure was the duration of locoregional control. Overall survival was also assessed. Results are presented in Table 6.

Table 6: Study 1: Clinical Efficacy in Locoregionally Advanced SCCHN

<table>
<thead>
<tr>
<th>Locoregional Control</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>0.68 (0.52–0.89)</td>
<td>0.74 (0.57–0.97)</td>
</tr>
</tbody>
</table>

CI = confidence interval

Study 2 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 either EU-approved cetuximab plus cisplatin or carboplatin and 5-FU, or cisplatin or carboplatin and 5-FU alone. Choice of cisplatin or carboplatin was at the discretion of the treating physician. Stratification factors were Karnofsky performance status >80 versus <80 and previous chemotherapy. Cisplatin (100 mg/m², Day 1) or carboplatin (AUC 5, Day 1) plus intravenous 5-FU (1000 mg/m²/day, 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 at a 400 mg/m² initial dose, followed by a 250 mg/m² weekly dose in combination with chemotherapy. Patients demonstrating at least stable disease on cetuximab in combination with chemotherapy were to continue cetuximab monotherapy at 250 mg/m² weekly, in the absence of disease progression or unacceptable toxicity after completion of 6 planned courses of platinum-based therapy. For patients where treatment was delayed because of the toxic effects of chemotherapy, weekly cetuximab was continued. If chemotherapy was discontinued for toxicity, cetuximab could be continued as monotherapy until disease progression or unacceptable toxicity.

Of the 442 randomized patients, the median age was 57 years, 90% were male, 88% were Caucasian, 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 arm switched to carboplatin during the treatment period. The main outcome measure of this trial was overall survival. Results are presented in Table 7 and Figure 1.

Table 7: Study 2: Clinical Efficacy in Recurrent Locoregional Disease or Metastatic SCCHN

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Progression-free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>0.80 (0.64, 0.98)</td>
<td>0.57 (0.46, 0.72)</td>
</tr>
</tbody>
</table>

CI = confidence interval

Platinum-based Therapy + 5-FU

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80 (0.64, 0.98)</td>
<td>0.57 (0.46, 0.72)</td>
</tr>
</tbody>
</table>

The main outcome measure of this trial was overall survival. Results are presented in Table 7 and Figure 1.

14.2 platinum-based therapy + 5-FU

Platinum-based Therapy + 5-FU

<table>
<thead>
<tr>
<th>Odds Ratio (95% CI)</th>
<th>CMH* test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35 (0.20, 0.60)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* CMH = Cochran-Mantel-Haenszel

ERBITUX (cetuximab) injection, for intravenous infusion

ERB-0002-USPI-20161011

ERBITUX (cetuximab) injection, for intravenous infusion

ERB-0002-USPI-20161011
In exploratory subgroup analyses of Study 2 by initial platinum therapy (cisplatin or carboplatin), for patients (N=284) receiving cetuximab plus cisplatin with 5-FU compared to cisplatin with 5-FU alone, the difference in median overall survival was 3.3 months (10.6 versus 7.3 months, respectively; HR 0.71; 95% CI 0.54, 0.93). The difference in median progression-free survival was 2.1 months (5.6 versus 3.5 months, respectively; HR 0.55; 95% CI 0.41, 0.73). The objective response rate was 39% and 23%, respectively (OR 2.18; 95% CI 1.29, 3.69). For patients (N=149) receiving cetuximab plus carboplatin with 5-FU compared to carboplatin with 5-FU alone, the difference in median overall survival was 1.4 months (9.7 versus 8.3 months; HR 0.99; 95% CI 0.69, 1.43). The difference in median progression-free survival was 1.7 months (4.8 versus 3.1 months, respectively; HR 0.61; 95% CI 0.42, 0.89). The objective response rate was 30% and 15%, respectively (HR 2.45; 95% CI 1.10, 5.46).

Study 3 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 received a 20-mg test dose of Erbitux on Day 1, followed by a 400 mg/m² initial dose, and 250 mg/m² weekly until disease progression or unacceptable toxicity. The median age was 57 years, 82% were male, 100% Caucasian, and 62% had a Karnofsky performance status of >80.

The objective response rate was 13% (95% confidence interval 7%–21%). Median duration of response was 5.8 months (range 1.2–5.8 months).

### 14.2 Colorectal Cancer

**Erbitux Clinical Trials in K-Ras Wild-type, EGFR-expressing, Metastatic Colorectal Cancer**

Study 4 was a randomized, open-label, multicenter, study of 1217 patients with EGFR-expressing, metastatic colorectal cancer. Patients were randomized (1:1) to receive either EU-approved cetuximab 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 (sites in Western Europe versus Eastern Europe versus other).

FOLFIRI regimen included 14-cycle days of irinotecan (180 mg/m² administered intravenously on Day 1), folinic acid (400 mg/m² [lomustine] or 200 mg/m² [L-ferum] administered intravenously on Day 1), and 5-FU (400 mg/m² bolus on Day 1 followed by 2400 mg/m² as a 46-hour continuous infusion). Cetuximab was administered as a 400 mg/m² initial dose on Day 1, followed by 250 mg/m² weekly administered 1 hour prior to chemotherapy. Study treatment continued until disease progression or unacceptable toxicity occurred. Of the 1217 randomized patients, the median age was 61 years, 60% were male, 86% were Caucasian, and 96% had a baseline ECOG performance status of 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 1079/1217 (89%) of the patients: 676 (63%) patients had K-Ras wild-type tumors and 403 (37%) patients had K-Ras mutant tumors where testing assessed for the K-Ras mutation status was available for 453/572 (79%) of the patients: 245 (54%) patients had wild-type tumors and 208 (46%) patients had mutant tumors.

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

<table>
<thead>
<tr>
<th></th>
<th>All Randomized</th>
<th>K-Ras Wild-type</th>
<th>K-Ras Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU-Approved Cetuximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus FOLFIRI (n=608)</td>
<td>343 (56)</td>
<td>371 (61)</td>
<td>165 (52)</td>
</tr>
<tr>
<td>FOLFIRI (n=609)</td>
<td>371 (56)</td>
<td>371 (61)</td>
<td>165 (52)</td>
</tr>
<tr>
<td>EU-Approved Cetuximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus FOLFIRI (n=320)</td>
<td>244 (76)</td>
<td>244 (76)</td>
<td>244 (76)</td>
</tr>
<tr>
<td>FOLFIRI (n=356)</td>
<td>244 (76)</td>
<td>244 (76)</td>
<td>244 (76)</td>
</tr>
<tr>
<td>EU-Approved Cetuximab</td>
<td></td>
<td></td>
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<tr>
<td>plus FOLFIRI (n=216)</td>
<td>189 (88)</td>
<td>189 (88)</td>
<td>189 (88)</td>
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<tr>
<td>FOLFIRI (n=187)</td>
<td>189 (88)</td>
<td>189 (88)</td>
<td>189 (88)</td>
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</tbody>
</table>

**Progression-Free Survival**

- **Number of Events (%)**
  - EU-Approved Cetuximab plus FOLFIRI: 491 (84%)
  - FOLFIRI: 509 (86%)

- **Median (months)**
  - EU-Approved Cetuximab plus FOLFIRI: 17 (17, 20)
  - FOLFIRI: 18 (17, 21)

- **HR (95% CI)**
  - EU-Approved Cetuximab plus FOLFIRI: 0.70 (0.57, 0.86)
  - FOLFIRI: 0.85 (0.74, 0.99)

- **p-value**
  - 0.0046

**Overall Survival**

- **Number of Events (%)**
  - EU-Approved Cetuximab plus FOLFIRI: 343 (56%)
  - FOLFIRI: 371 (56%)

- **Median (months)**
  - EU-Approved Cetuximab plus FOLFIRI: 19.5 (18.5, 20.6)
  - FOLFIRI: 23.5 (23.5, 24.5)

- **HR (95% CI)**
  - EU-Approved Cetuximab plus FOLFIRI: 0.71 (0.54, 0.93)
  - FOLFIRI: 0.85 (0.74, 0.99)

- **p-value**
  - 0.0358

**Objective Response Rate**

- **OR (95% CI)**
  - EU-Approved Cetuximab plus FOLFIRI: 0.46 (0.42, 0.50)
  - FOLFIRI: 0.43 (0.39, 0.46)

- **p-value**
  - 0.28

Based on the Stratified Log-rank test.

**Post-hoc updated OS analysis, results based on an additional 162 events.**

Study 5 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 plus best supportive care (BSC) or BSC alone. Erbitux was administered as a 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity.

Of the 572 randomized patients, the median age was 63 years, 64% were male, 90% were Caucasian, 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 453/572 (79%) of the patients: 245 (54%) patients had K-Ras wild-type tumors and 208 (46%) patients 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 [see Warnings and Precautions (5.7)].

The main outcome measure of the study was overall survival. Results are presented in Table 9 and Figure 3.

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

<table>
<thead>
<tr>
<th></th>
<th>All Randomized</th>
<th>K-Ras Wild-type</th>
<th>K-Ras Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erbitux plus BSC (N=227)</td>
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<td></td>
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<tr>
<td>BSC (N=235)</td>
<td>6.1 (4.6, 8.6)</td>
<td>6.1 (4.6, 8.6)</td>
<td>6.1 (4.6, 8.6)</td>
</tr>
</tbody>
</table>

**Median (months)**

- **(95% CI)**
  - EU-Approved Cetuximab plus BSC: (6.4, 6.7)
  - FOLFIRI plus BSC: (7.0, 10.3)

- **HR**
  - EU-Approved Cetuximab plus BSC: 0.43 (0.39, 0.47)
  - FOLFIRI plus BSC: 0.43 (0.39, 0.47)

- **p-value**
  - 0.0046

Based on the Stratified Log-rank test.

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

ERBITUX® (cetuximab) injection, for intravenous infusion

ERB-0002-USPI-20161101

ERBITUX® (cetuximab) injection, for intravenous infusion

ERB-0002-USPI-20161101
Study 6 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 plus irinotecan (218 patients) or Erbitux monotherapy (111 patients). Erbitux was administered as a 400 mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. In the Erbitux plus irinotecan arm, irinotecan was added to Erbitux using the same dose and schedule as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline Karnofsky performance status ≥80. Approximately two-thirds had previously failed oxaliplatin treatment.

The efficacy of Erbitux plus irinotecan or Erbitux monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux plus irinotecan, the objective response rate was 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving Erbitux monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%), median duration of response 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 monotherapy arm of the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

Erbitux® (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid containing no preservatives.

NDC 66733-948-23   100 mg/50 mL, single-use vial, individually packaged in a carton
NDC 66733-958-23   200 mg/100 mL, single-use vial, individually packaged in a carton

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

17 PATIENT COUNSELING INFORMATION

Advise patients:
- To report signs and symptoms of infusion reactions such as fever, chills, or breathing problems.
- Of the potential risks of using Erbitux during pregnancy or nursing and of the need to use adequate contraception in both males and females during and for 6 months following the last dose of Erbitux therapy.
- That nursing is not recommended during, and for 2 months following the last dose of Erbitux therapy.
- To limit sun exposure (use sunscreen, wear hats) while receiving and for 2 months following the last dose of Erbitux.

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Lilly

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