Drug Monograph

A - Drug Name

cetuximab

COMMON TRADE NAME(S): Erbitux®

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B - Mechanism of Action and Pharmacokinetics

Cetuximab is a recombinant, human (IgG1)/mouse (Fv regions) chimeric monoclonal antibody which binds specifically to the epidermal growth factor receptors (EGFR) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. This blocks phosphorylation and activation of receptor-associated kinases, which results in inhibition of cell growth, induction of apoptosis, and decreased vascular endothelial growth factor production.

EGFR is expressed in normal tissues such as skin, mucosa and kidney as well as in common epithelial tumours such as NSCLC, colorectal cancer and head and neck tumours. The EGFR signaling cascade results in RAS protein activation, which contributes to K-RAS wild-type tumour growth. Tumours with K-RAS mutations appear to be unaffected by EGFR inhibition (i.e., RAS proteins are active regardless of EGFR activation).

Distribution	Cetuximab exhibits non-linear pharmacokinetics. AUC increased in a greater than dose-proportional manner as the dose increased from 20 to 200 mg/m^2. Steady state is reached by the third weekly infusion.	
	Cross blood brain barrier?	Unknown
	PPB	No information found (unlikely)
Metabolism	Cetuximab is metabolized and eliminated via the reticuloendothelial system.	

	Active metabolites	No
	Inactive metabolites	No
Elimination	Clearance decreases with increasing dose.	
	Half-life	112 hours (mean; 400mg/m^2 dose followed by 250mg/m^2 weekly)
	Urine	No

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C - Indications and Status

Health Canada Approvals:

- Colorectal cancer
- Head and neck cancer

Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Skin cancer

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following table contains adverse effects reported mainly in patients with advanced CRC treated with cetuximab plus best supportive care, unless otherwise specified. Severe or life-threatening adverse effects from other studies or post-marketing are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Hearing impaired (2%)	E D
Cardiovascular	Arrhythmia (2%)	E
	Arterial thromboembolism (rare)	E
	Hypertension (3%)	E
	Hypotension (4%)	E
	Sudden death (2%) (head and neck only)	E
	Venous thromboembolism (3%)	E
Dermatological	Alopecia (7%)	E
	Hand-foot syndrome (4%)	E
	Hypertrichosis (4%) (with FOLFIRI)	E
	Nail disorder (28%)	E
	Paronychia (20%) (with FOLFIRI)	E
	Rash (95%) (acneiform; 18% severe)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Abdominal pain (59%)	E
	Anorexia (68%)	E
	Ascites (6%)	E D
	Constipation (51%)	E
	Diarrhea (39%)	E
	Dry mouth (14%)	E
	Dysphagia (7%)	E
	Flatulence (4%)	E
	GI obstruction (6%)	E
	GI perforation (rare)	E
	Mucositis (31%)	E
	Nausea, vomiting (61%) (5% severe)	E
General	Fatigue (91%) (30% severe)	E
	Flu-like symptoms (25%)	E
Hematological	Hemorrhage (9%) (including GI)	E
Hepatobiliary	↑ LFTs (11%)	E
	Pancreatitis (rare)	E

Hypersensitivity	Infusion related reaction (20%) (4% severe)	I
Immune	Antibody response (<5%) (anti-cetuximab antibody response)	D
Infection	Infection (40%) (9% severe)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (3%) (high or low K, Ca)	E
	Hyperglycemia (9%) (with radiation)	D
	↓ Mg (43%) (17% severe)	E D
Musculoskeletal	Musculoskeletal pain (14%)	E
Nervous System	Dizziness (10%)	E
	Dysgeusia (10%)	E
	Headache (38%)	E
	Insomnia (30%)	E
	Mood changes (17%) (including confusion)	E
	Neuropathy (49%) (1% severe)	E D
Ophthalmic	Conjunctivitis (3%)	E
	Eye disorders (9%) (including keratitis, dry eye)	E
Renal	Creatinine increased (<1%; may be severe)	E
Respiratory	Cough, dyspnea (48%) (16% severe)	E
	Pleural effusion (2%)	E
	Pneumonitis (<0.3%)	E
	Rhinitis (8%)	I E
Urinary	Urinary symptoms (6%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for cetuximab include rash, fatigue, anorexia, nausea, vomiting, abdominal pain, constipation, neuropathy, cough, dyspnea, hypomagnesemia and infection.

As with all therapeutic proteins, there is potential for **immunogenicity**. However, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumour activity of cetuximab.

Hypomagnesemia is severe in 17%. Magnesium supplementation may correct accompanied hypocalcemia, as parathyroid hormone release and its ability to mobilize calcium from the bone are

impaired in the setting of hypomagnesemia. Electrolyte repletion was necessary in some patients, and intravenous replacement was required in severe cases. Monitoring during and after cetuximab treatment is recommended.

Severe **infusion reactions** occur in up to 3% of patients, may be fatal especially in patients with head and neck cancer receiving radiation, and can occur despite use of premedication. Although 90% occur with the first infusion, patients should be observed for at least 1-hour after each cetuximab infusion. Late-onset symptoms (i.e., several hours after infusion) have been reported with subsequent infusions. Severe infusion reactions require immediate discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, vasopressors and oxygen should be available for use in the treatment of such reactions.

Anaphylactic reactions to cetuximab can occur in patients without previous cetuximab exposure. There is an increased risk for anaphylactic reactions in patients with a history of tick bites, red meat allergy, or in the presence of IgE antibodies directed against galactose-alpha-1,3-galactose which is present on cetuximab.

Interstitial lung disease (ILD) is rare but can be fatal. Onset is variable. Hold and investigate any acute onset or worsening respiratory symptoms. If a diagnosis of ILD is made, discontinue cetuximab and institute appropriate therapy.

Dermatologic toxicities, especially acneiform rash, are common and usually develop within the first two weeks of therapy. Complications including S. aureus sepsis and abscesses requiring incision and drainage can occur. If severe acneiform rash develops, modify the dose of subsequent cetuximab infusions. UV exposure can exacerbate any skin reaction that may occur. Patients should use sun protection while receiving cetuximab and for 2 months after treatment completion. Refer to the Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies (Melosky 2009).

Life-threatening mucocutaneous skin reactions, including Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TENS) have been reported.

Cetuximab given in combination with radiation results in incremental fatigue, fever, headache, chills, infection, pain, allergic reactions, hypotension, syncope, GI side effects, weight loss, hyperglycemia, abnormal LFTs, pain, rash and late radiation effects (skin, mucosa, salivary glands).

Cetuximab given in combination with FOLFIRI increased the risk of cardiac events and palmar-plantar erythrodysesthesia syndrome.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

RAS wild type status should be confirmed by validated test prior to starting treatment for mCRC.

Premedications (prophylaxis for infusion reaction):

- H1-receptor antagonist (e.g. diphenhydramine 50 mg IV) 30-60 minutes prior to the dose.
- Corticosteroid IV 30-60 minutes prior to the dose.
- Consider discontinuing pre-medications after the 2nd infusion based on clinical judgment and the presence/severity of IR.

Other Supportive Care:

- Patients should use sun protection while receiving cetuximab and for 2 months after treatment completion.
- Consider pre-emptive therapy for EGFR inhibitor-related skin toxicity; the following was shown to be of benefit with panitumumab treatment, starting the day before treatment and continued until week 6. (Lacouture et al, 2010):
    - Skin moisturizer applied to the face, hands, feet, neck, back and chest in the morning
    - Sunscreen to exposed areas (SPF $\geq$ 15, UVA and UVB) before going outdoors
    - Hydrocortisone 1% cream to the face, hands, feet, neck, back and chest at bedtime
    - Doxycycline (or minocycline) PO
- Refer to the Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies. (Melosky et al, 2009)

Adults:

The recommended dose of cetuximab in combination or as monotherapy is:

Loading dose:

Intravenous: 400 mg/m² single dose

(for head and neck cancer, give 1 week prior to radiation start date)

Maintenance dose:

Intravenous: 250 mg/m² Weekly

(for head and neck cancer complete infusion 1 hour prior to that day's radiation)

Dosage with Toxicity:

Dose Level	Cetuximab Dose (mg/m² weekly)
0	250
-1	200
-2	150
-3	Discontinue

Toxicity	Action	Next cycle
Pneumonitis	Hold and investigate	Discontinue if confirmed.
Keratitis	Hold and refer to ophthalmologist	Consider discontinuation.

Dosage modification for skin toxicity:

Grade 3 or 4 Rash	Action	Outcome	Cetuximab Dose
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Resume at same dose
		No improvement	Discontinue
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Resume at 1 dose level ↓
		No improvement	Discontinue
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Resume at 1 dose level ↓
		No improvement	Discontinue
4th occurrence OR any occurrence of SJS/TENS	Discontinue		

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • The infusion may be restarted at a slower rate (50% of the rate at which the IR occurred) once symptoms have resolved.	• Re-challenge with a reduced infusion rate of 50% at which the infusion reaction occurred.
3 or 4	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate, unless a serious reaction occurred (i.e., vital signs compromised; anaphylaxis).	• Permanently discontinue (do not re-challenge).

Dosage with Hepatic Impairment:

Population pharmacokinetics suggest no significant impact.

Dosage with Renal Impairment:

Population pharmacokinetics suggest no significant impact.

Dosage in the elderly:

No dosage adjustment is required in colorectal cancer. No overall differences in safety or efficacy were observed in patients ≥ 65 years of age compared to younger patients. Insufficient patients have been enrolled in head and neck studies to draw firm conclusions.

Dosage based on gender:

Females have lower cetuximab clearance, but dose modifications are not required.

Children:

The safety and efficacy of cetuximab in pediatric patients have not been studied.

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F - Administration Guidelines

- Do not shake or further dilute the solution.
- DO NOT administer as an IV push or bolus.
- Transfer undiluted solution into a compatible empty infusion container.
- Cetuximab is compatible with:
  - glass,
  - polyolefin, polyethylene, ethylene vinyl acetate (EVA), DEHP plasticized PVC, or PVC bags,
  - polyethylene, EVA, PVC, polybutadiene or polymethane infusion sets, and
  - polyethersulfone, polyamide or polysulfone in-line filters.
- If given with irinotecan, give cetuximab first.
- If given with radiation (for head and neck cancer), give cetuximab 1 week prior to radiation start date. For maintenance, complete cetuximab infusion 1 hour prior to that day's radiation.
- Administer the undiluted solution via a low protein binding 0.22-micrometer in-line filter, piggybacking to the patient’s infusion line.
- Infuse initial loading dose over 2 hours, and maintenance dose over 1 hour (maximum rate 10 mg/min). (May require infusion at slower rate in those who experienced infusion reactions).
- Prime administration line with drug solution before infusion. May use NS to flush line at the end of infusion.
- A 1-hour observation period is recommended following each cetuximab infusion. Longer observation periods may be required in those who experienced infusion reactions.
- Should not be mixed or diluted with other drugs.
- Store unopened vials at 2-8°C.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Cetuximab is not indicated for the treatment of colorectal cancer in patients with RAS mutations or RAS unknown status.
- Patients with a history of, or pre-existing keratitis, dry eyes or contact lens use
- Patients with poor performance status, or cardiopulmonary disease are at increased risk of severe hypersensitivity
- Cetuximab plus radiation therapy for head and neck cancer should be used with caution in patients who are over age 65, have poor performance status, known history of coronary artery disease, arrhythmias, congestive heart failure or receiving cardiotoxic agents as fatal events have been reported.

Other Drug Properties:

- Carcinogenicity: Unknown
  Cetuximab has not been tested for carcinogenicity, but is not mutagenic or clastogenic.

Pregnancy and Lactation:

- Fetotoxicity: Yes
- Crosses placental barrier: Yes
  (IgG molecules)
- Abortifacient effects: Yes
  Cetuximab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended during cetuximab therapy and for at least **60 days** after the last dose.
- Fertility effects: Unknown

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H - Interactions

No drug interactions of clinical significance have been reported. There is no evidence of any pharmacokinetic interaction between cetuximab and irinotecan.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Radiation	Additive mucocutaneous toxicity	Unknown	Caution; monitor for toxicity.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Electrolytes, including serum magnesium, potassium and calcium	Baseline, weekly, and monthly for 2 months following completion of therapy
CBC	Baseline and as clinically indicated
Renal function	Baseline and as clinically indicated
Clinical toxicity assessment for infusion reactions, skin, nail, cardiac, thromboembolism, GI, hypersensitivity, respiratory symptoms, fatigue and keratitis	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Cetuximab and Radiation - Locally Advanced Squamous Cell Carcinoma of the Head and Neck
- Cetuximab with Irinotecan - Metastatic Colorectal, Small Bowel, or Appendiceal Cancer
- Cetuximab - In Combination with Encorafenib for Previously Treated Metastatic Colorectal Cancer

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K - References

Lacouture, ME, Mitchell EP, Piperdi B et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010; 28: 1351-7.

Melosky B, Burkes R, Rayson D, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Current Oncology 2009; 16(10): 14-24.

Prescribing Information: Erbitux® (cetuximab). ImClone LLC, September, 2021.

Product Monograph: Erbitux® (cetuximab). Bristol Myers Squibb Canada, November 2016.

Product Monograph: Erbitux® (cetuximab). Eli Lilly Canada Inc, August 13, 2020.

Summary of Product Characteristics: Erbitux® (cetuximab). Merck Serono Ltd, May 2022.

Tran VL, Novell A, Tournier N, et al. Impact of blood-brain barrier permeabilization induced by ultrasound associated to microbubbles on the brain delivery and kinetics of cetuximab: An immunoPET study using ^{89}Zr-cetuximab. J Control Release. 2020 Dec 10;328:304-312.

July 2023 Updated MOA/pharmacokinetics, indications, adverse effects, dosing, administration, special precautions, interactions, and monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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