Cetuxim

Cetuximab injection

COMPOSITION

Cetuxim Injection: Each vial contains Cetuximab INN 100 mg (5 mg/ml).

PHARMACOLOGICAL INFORMATION

Description:

Cetuxim injection (Cetuximab) 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. Cetuxim injection is supplied at a concentration of 100 mg/20 mL single-use vials.

Pharmacological Action

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum. Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. In vitro assays and in vivo animal studies have shown that binding of Cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Signal transduction through the EGFR results in activation of wild type K-Ras protein. However, in cells with activating K-Ras somatic mutations, the mutant K-Ras protein is continuously active and appears independent of EGFR regulation.In vitro, Cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types.

Pharmacokinetics

Cetuximab 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/m as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of the 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.

CLINICAL INFORMATION

Therapeutic Indications

- **Squamous Cell Carcinoma of the head and Neck**
  Cetuxim injection is indicated in combination with radiation therapy for the initial treatment of locally orregionally advanced squamous cell carcinoma of the head and neck. Cetuxim injection 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. Cetuxim injection, 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
- **K-Ras Mutation-negative, EGFR-expressing Colorectal Cancer**
  Cetuxim injection is indicated for the treatment of K-Ras mutation-negative (wild-type), epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer (mCRC) as determined by FDA-approved tests for this use
  - in combination with FOLFIRI (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

Dosage and Administration

- **Squamous Cell Carcinoma of the head and Neck**
  Cetuximab 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 Cetuximab 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 Cetuximab administration 1 hour prior to radiation therapy or platinum-based therapy with 5-FU.

  Cetuximab 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 / min infused over 60 minutes (maximum infusion rate 10 mg/min) until disease progression or unacceptable toxicity
- **Colorectal Cancer**
  - Determine K-Ras mutation and EGFR-expression status using FDA-approved tests prior to initiating treatment. Only patients whose tumors are K-Ras mutation-negative (wild-type) should receive Cetuxim injection
  - 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 Cetuximab 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 Cetuximab administration 1 hour prior to FOLFIRI.

Recommended Premedication

Premedicate with an H_1 antagonist (eg, 50 mg of Diphenhydramine) intravenously 30-60 minutes prior to the first dose; premedication should be administered for subsequent Cetuximab doses based upon clinical judgment and presence/severity of prior infusion reactions

Method of administration

Do not administer Cetuxim injection 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.

Instructions for Use and Handling

Cetuxim injection (5 mg/mL) may be administered via a gravity drip, an infusion pump or a syringe pump method. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 9 mg/mL (0.9%) solution for injection at the end of infusion.

Product is for single use in one patient only. Discard any residue.

Cetuxim injection 5 mg/mL is compatible with:

- Polyethylene (PE), Ethyl Vinyl Acetate (EVA) or Polyvinyl Chloride (PVC) bags
- Polyethylene (PE), Polyurethane (PUR), Ethyl Vinyl Acetate (EVA), Polyolefine Thermoplastic (TP) or Polyvinyl Chloride (PVC) infusion sets
- Polypropylene (PP) syringes for syringe pump

Cetuxim injection 5 mg/mL must be prepared as follows:

For administration with infusion pump or gravity drip (diluted with sterile sodium chloride 9 mg/mL (0.9%) solution): Take an infusion bag of adequate size of sterile sodium chloride 9 mg/mL (0.9%) solution. Calculate the required volume of Cetuxim injection. Remove an adequate volume of the sodium chloride solution from the infusion bag, using an appropriate sterile syringe with a suitable needle. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Cetuxim injection from a vial. Transfer the Cetuxim injection into the prepared infusion bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with the diluted Cetuxim injection before starting the infusion. Use a gravity drip or an infusion pump for administration.

For administration with infusion pump (undiluted): Calculate the required volume of Cetuxim injection. Take an appropriate sterile syringe (minimum 50 mL) and attach a suitable needle. Draw up the required volume of Cetuxim injection from a vial. Transfer the Cetuxim injection into a sterile evacuated container or bag. Repeat this procedure until the calculated volume has been reached. Connect the infusion line and prime it with Cetuxim injection before starting the infusion. Use an infusion pump for administration.

For administration with a syringe pump: Calculate the required volume of Cetuxim injection. Take an appropriate sterile syringe and attach a suitable needle. Draw up the required volume of Cetuxim injection from a vial. Remove the needle and put the syringe into the syringe pump. Connect the infusion line to the syringe, section and start the infusion after priming the line with Cetuxim injection or sterile sodium chloride 9 mg/mL (0.9%) solution. If necessary, repeat this procedure until the calculated volume has been infused.

Use in Specific Population

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Cetuximab in pregnant women. Based on animal models, EGFR 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, Cetuximab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Cetuximab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Cetuximab secreted in human milk. IgG antibodies, such as Cetuximab, 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 Cetuximab, 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 nursing should not be resumed earlier than 60 days following the last dose of Cetuximab.

Pediatric Use

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

Contraindication

None

WARNINGS AND PRECAUTIONS

Infusion Reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of Cetuximab included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Cardiopulmonary Arrest

Carefully consider use of Cetuximab 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 Cetuximab.

Pulmonary Toxicity

Cetuximab for acute onset or worsening of pulmonary symptoms. Permanently discontinue Cetuximab for confirmed ILD.

Dermatologic Toxicity

Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example, S. aureus sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis/ulcerative keratitis with decreased visual acuity, cheilitis), and hypertrichosis occurred in patients receiving Cetuximab therapy.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections

- Infusion reactions
- Cardiopulmonary arrest
- Pulmonary toxicity
- Dermatologic

The most common adverse reactions in Cetuximab clinical trials (incidence ≥25%) include cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. The most serious adverse reactions with Cetuximab are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus.

Drug Interaction

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

PHARMACEUTICAL INFORMATION

Storage Condition

Store the vial in original carton at 2˚C to 8˚C. Protect from light. Do not freeze. Keep out of the the reach of children.

Presentation & Packaging

Cetuxim Injection: Each commercial box contains 1 vial of 20 ml solution.

Manufactured By
BEACON Pharmaceuticals Limited
Mymensingh, Bangladesh

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