CIMAhern™

Injection solution

Formulation
CIMAhern™ is formulated as a colorless sterile solution in 10 mL of water for injection. Each 10 mL vial contains:

Nimotuzumab
50.0 mg
Dibasic sodium phosphate (Na₂HPO₄)
18.0 mg
Monobasic sodium phosphate (NaH₂PO₄)
1.7 mg
Sodium chloride
60.0 mg
Polysorbate 80
0.3 mg
Water for injection
ad 10 mL

Description
Nimotuzumab (CIMAhern™) is a recombinant humanized monoclonal antibody that binds to the extracellular domain of human epidermal growth factor receptor (EGFR). The humanized monoclonal antibody was obtained by selecting the complementarity determining regions (CDRs) of the murine IgG2a monoclonal antibody (or EGFR) to a human framework for computer modeling. A reassigned antibody was constructed using the light and heavy chains (RS1 and RS2, respectively) as human immunoglobulin frameworks for CDR grafting. CIMAhern™ is produced through mammalian cell culture of non-ratified NCS cells and has a molecular weight of 151 KD.

Clinical pharmacology
Nimotuzumab binds with intermediate affinity and high specificity to the extracellular domain of epidermal growth factor receptor (EGFR, HER1). Nimotuzumab blocks the binding of the EGFR and other ligands, such as transforming growth factors, alphas, etc., to its receptor and inhibits its activity in various cancer cell types. Nimotuzumab has a potent anti-angiogenic, anti-proliferative and pro-apoptotic effect, and also decreases motility, cell invasion and metastasis in those tumors that overexpress the EGFR.

EGFR is expressed in cells from all three embryonic layers, especially in cells of epithelial origin (skin, respiratory tract, gastrointestinal tract, urinary tract and liver). EGFR is present in various tumor tissue and in vitro. EGFR protein was elevated in tumors as compared to normal tissue. The combination of antibody in tumors is highest at 24 hours after injection. In tumors the volume of the central compartment (Vc) is expressed in mg per 100 mL. The value of Vc in tumors is 27.5 to 77.5 mg per 100 mL 40 to 60 mg/kg dose, respectively. Nimotuzumab is mainly distributed in liver, kidneys, skin, spleen and bladder.

Nimotuzumab is eliminated in the bile, feces, urine, heart, skin, spleen and bladder. Most of the antibodies were undetectable in bile. The median time to complete clearance was 115.8 days. The approximate time of elimination was between 115 and 150 days.

Indication
- Treatment of advanced stages head and neck cancers, including nasopharyngeal carcinoma
- Treatment of advanced stages breast and colon cancers
- Treatment of high grade astrocytomas as monotherapy or in combination therapy
- Treatment of glioblastomas multiforme in combination with radiation therapy in adults
- Treatment of patients with inoperable esophageal malignancies with epithelial origin

Dosage
Advanced Head and Neck Cancers and Nasopharyngeal Carcinoma
The recommended dose of CIMAhern™ is 10 mg/m² weekly for 6 weeks in combination with radiotherapy and/or chemotherapy. The recommended dose of CIMAhern™ for nasopharyngeal carcinoma is 200 mg/m² once a week for 6 weeks in combination with radiotherapy. Subsequently, it will be administered as a dose of 200 mg CIMAhern™ every 15 days (maintenance dose) until the patient’s general condition permits.

Glioma
The recommended dose of CIMAhern™ for glioma in adults is 200 mg/m² every 6 weeks in combination with conventional treatment. Subsequently, it will be administered as a dose of 200 mg CIMAhern™ every 15 days (maintenance dose) until the patient’s general condition permits. Dosage for glioma in children & adolescents: monotherapy in two consecutive phases, induction phase and consolidation phase. During induction phase, CIMAhern™ is given at 150 mg/m² weekly for 6 weeks. After induction, patient without progressive disease upon 8th week evaluation will be treated in the consolidation phase where CIMAhern™ is given at 150 mg/m² weekly for 6 weeks until disease progression.

Inoperable Esophageal Malignancy with Epithelial Origin
The recommended dose of CIMAhern™ for esophageal cancer is 200 mg administered once a week for 6 weeks concurrently with standard radiotherapy and/or chemotherapy.

Administration
The recommended dosage of CIMAhern™ (Nimotuzumab or HR-1) in each indication is administered as continuous intravenous (IV) infusion combined with a standard radiotherapy and/or chemotherapy. Nimotuzumab is diluted in normal saline (0.9% solution and administered intravenously within 60 minutes for adult patients and 30 minutes for pediatric/adult patients). Premedication with diphenhydramine is recommended to minimize possible infusion reaction especially for patients having history of hypersensitivity reaction to any monoclonal antibody or any medicinal products.

Contraindications
No contraindications have been reported to date.

Warnings and precautions
1. CIMAhern™ (Nimotuzumab) should be administered with caution in patients who have previously received treatment with the murine monoclonal antibody or epidermal growth factor receptor or patients with previous notification of having hypersensitivity to this product or other products derived from NCS mammalian cells or any component of this product. CIMAhern™ (Nimotuzumab) should be used with caution in patients with chronic diseases in a decompensated phase, such as cardiac dysfunction, diabetes mellitus or other severe hyperventilation in patients with history of severe allergy reaction.
2. The product should be applied under the supervision of skilled clinical doctors.

Use in pregnancy and lactation
Use in Pregnancy
Effects of Nimotuzumab on pregnancy have not been studied. However, animal studies have shown that at the embryonic stage, last of EGFR can cause lack of maturation of the epidermal and postnatal development. EGFR has been implicated in the control of preterm development and hence may be essential for normal organogenesis, proliferation and differentiation in the developing embryo. Human IgG1 is known to cross the placental barrier; therefore the antibody has the potential to be transmitted to the mother's or father's body. The use of Nimotuzumab during pregnancy is not recommended. The antibody should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit outweighs the potential risk to the fetus. If the patient becomes pregnant while receiving this drug, she should be informed of the potential hazard to the fetus and the potential risk of loss of the pregnancy.

Use in Lactation
Nimotuzumab is secreted in human milk. Therefore it is not recommended to use in lactating women. No recommendation is made on the potential benefit versus risk of administering Nimotuzumab to nursing mothers.

Pediatric use
A phase II clinical study in pediatric patients with brain tumors is done and showed no significant adverse events related to Nimotuzumab. Efficacy in heavily pretreated relapsed high grade gliomas in children and adolescents has been demonstrated in the phase II trial. The repeated application of Nimotuzumab as monotherapy was well tolerated and safe. The clinical deteriorations were mostly associated with progression of the tumor disease, tumor progression or, rarely, with another concomitant disease. In particular no allergic reactions or severe side effects or gastrointestinal toxicities were observed. No safety concerns arose from laboratory tests, vital signs, or physical examination findings. No severe hematological or non-hematological side effects were associated with the administration of Nimotuzumab in childhood malignancies. A phase III trial of newly diagnosed diffuse intrinsic pontine glioma in pediatric/adult is currently ongoing.

Adverse reactions
Common adverse events with recommended dose reported following administration of Nimotuzumab that are at least possibly related to Nimotuzumab include chills, fatigue, headache, nausea, paresthesias, tremor and vomiting. In the pediatric trial, non-serious adverse events consisted at least possibly related to Nimotuzumab included erythema, fatigue, headache, leucocytosis, nausea, paresthesias, and vomiting. Rare adverse events reported were asthenia, anaphylaxis, anorexia, dehydration, hematoma, and elevated liver function enzymes. In clinical experience, potentially fatal allergic reaction was very rarely reported. This event includes rapid and severe hypotension and urtica.

Drug interactions
The interaction of Nimotuzumab with other cytostatic drugs has not been evaluated in clinical trials, and it therefore does not appear to be any significant interaction with the administered gemcitabine. An ongoing study in colorectal cancer in which Nimotuzumab is being administered with 5-fluorocitax has not demonstrated any unwanted effects to date. Synergistic effects and potentiation of the anti-tumor activity had already been shown when other EGFR inhibitors have been used in combination with chemotherapy.

Overdose
A phase I study conducted in Canada has demonstrated that doses up to 800 mg/m² are safe and well tolerated in humans.

Preparation for administration
1. Do not shake the content of the vial. A vigorous shaking could denature the protein and affect the biological activity of the product.
2. Product should be inspected visually for particulates and discolouration prior to administration, if these are present do not use the product.
3. Use a syringe and tubing with appropriate accessory equipment. Do not remove the cap from the vial containing CIMAhern™ (Nimotuzumab) and clean the top of the vial with antiseptic. Screw the needle into the vial and extract the contents.
4. The CIMAhern™ (Nimotuzumab) at the selected dosage should be diluted in 200 mL of solution (0.9%)

Storage conditions
1. CIMAhern™ (Nimotuzumab) should be stored in refrigerator at 2-8°C. The biological and chemical stability may be lost after freezing and thawing. Do not freeze or thaw.
2. The antibody diluted in the saline buffer is physically and chemically stable up to 72 hours when stored at room temperature (25 ± 3°C). Nimotuzumab diluted saline buffer may not be active beyond these conditions, the solution should be discarded and fresh solution should be prepared for infusion.

Shelf life
Please refer to expiry date on label / carton.

Presentation
1 box contain 4 vials of Solution for Injection. Each 15 mL vial contains Nimotuzumab 5 mg/m² Reg. No. R-2007A2558

ON PRESCRIPTION MEDICATION
Date of Revision of Package Insert : 19 November 2015
Manufactured by:
Center of Molecular Immunology (CIM)
Calle 216 n° 15, Asunciòn, Plaza C. Havan, Nueva de Cuba

Kelermann:
1. Warns des Puffers
2. Labor, Logo Kalbe
3. Anti hervor
4. HVR 60 g/m²
5. Size
6. Cetaka

Kolom Perusahaan:
GMC OGC Market Roading IGK* For internal purpose only (en-large) 21-02-2010 for inter-office