# CIMAher™
# Nimotuzumab

**Injection solution**

**Formulation**

**CIMAher™** 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 ($Na_2HPO_4$) | 18.0 mg |
| Monobasic sodium phosphate ($NaH_2PO_4$) | 4.5 mg |
| Sodium chloride | 86.0 mg |
| Polysorbate 80 | 2.0 mg |
| Water for injection | ad 10 ml |

**Description**

**CIMAher™** (Nimotuzumab) is a recombinant humanized monoclonal antibody that binds to the extracellular domain of human epidermal growth factor receptor (EGFR). The humanized antibody (IgG1) was obtained by transplanting the complementarity determining regions (CDRs) of the murine IgG2a monoclonal antibody (ior egf/r3) to a human framework assisted by computer modeling. A reshaped antibody was constructed using the light and heavy chains (REl and Eu, respectively) as human immunoglobulin framework for CDR-grafting. **CIMAher™** is produced through mammalian cell culture of non-secreting NSO 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, c-Erb-1). Nimotuzumab blocks the binding of the EGF and other ligands, such as transforming growth factor-alpha, etc., to its receptor and inhibits *in vivo* and *in vitro* tumor cell growth. Nimotuzumab and has a potent anti-angiogenic, anti-proliferative and pro-apoptotic effects, and also decrease motility, cell invasion and metastasis in those tumors that overexpress the EGFR.

EGFR is expressed in cells from all three embryonic layer cells especially in cells of epithelial origin (skin, respiratory tract, gastrointestinal tract, urinary tract and liver). EGFR is present in wide diversity of human tumors of epithelial origin like non small cell lung cancer (NSCLC), head and neck, pancreatic, colon, breast, kidney, ovarian and bladder carcinomas. It is also overexpressed in glioma and uterine cervical cancers.

**Pharmacokinetics**

Nimotuzumab administered in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. Following a 30 minute infusion the area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 50 to 400 mg. Evidence from an animal pharmacokinetic study indicates that the concentration of the antibody in tumors is highest at 24 hours after injection. In humans the volume of the central compartment ($V_c$) for Nimotuzumab ranged from 2.3 to 7.2 l and maximal concentration ($C_{max}$) was 27 to 57 ng/ml for 50 to 400 mg doses, respectively. Nimotuzumab is mainly distributed in liver, spleen, heart, kidney, and bladder. Most of the antibodies were uptake by liver.

Nimotuzumab clearance (CL) decreased from 1.08 to 0.34 ml/h/kg as the dose increased from 50 to 200 mg, and at doses >200 mg, it appeared to plateau. Pharmacokinetic analysis of plasma clearance curves showed terminal half-life times ($t_{1/2b}$) for 50, 100, 200, and 400 mg doses of 62, 82, 302, and 304 hours, respectively. Under normal physiological conditions, the percentage of injectied dosage discharged through urinary tract are 21.1% for 50 mg, 28.20% for 100 mg, 27.36% for 200 mg, 33.57% for 400 mg.

**Indication**

- Treatment of advanced stages head and neck cancers, including nasopharyngeal carcinoma
- Treatment of high-grade astrocytoma as monotherapy, in children refractory to oncospecific treatment
- Treatment of glioblastoma multiforme in combination with radiation theraphy in a adults
- Treatment of patients with inoperable esophageal malignancy with epithelial origin

**Dosage**

***Advanced Head and Neck Cancers and Nasopharyngeal Carcinoma***

The recommended dose **CIMAher™** for head and neck cancer is 200 mg once a week for 6 weeks in combination with radiotherapy and/or chemotherapy. The recommended dose **CIMAher™** for nasopharyngeal carcinoma is 200 mg once a week for 8 weeks in combinations with radiation.
Subsequently, it will be administered a dose of 200 mg **CIMAher™** every 15 days (maintenance dose) until the patient's general condition permits.

***Glioma***

The recommended dose **CIMAher™** for glioma in adults is 200 mg weekly in combination with conventional radiation treatment. Subsequently, it will be administered a dose of 200 mg **CIMAher™** 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, **CIMAher™** is given at 150 mg/m$^2$ BSA weekly for 6 weeks. After induction, patient without progressive disease upon 8$^{th}$ week evaluation will be treated in the consolidation phase where **CIMAher™** is given at 150 mg/m$^2$ BSA every 3 weeks until disease progression.

***Inoperable Esophageal Malignancy with Epithelial Origin***

The recommended dose **CIMAher™** for esophageal cancer is 200 mg administered once a week during 6 weeks concomitantly with standard radiotherapy and/or chemotherapy.

**Administration**

The recommended dosage of **CIMAher™** (Nimotuzumab or h-R3) in each indication is administered as continuous intravenous (IV) infusions combination with a standard radiotherapy and/or chemotherapy. Nimotuzumab is diluted in 250 ml of sodium chloride 0.9% solution and administered intravenously within 60 minutes for adult patients and 30 minutes for pediatric/adolescent patients. Pretreatment 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.

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**Warnings and precautions**

1. **CIMAher™** (Nimotuzumab) should be administered with cautions in patients who have previously received treatment with the murine monoclonal antibody ior egf/r3, patients with previous notification of having hypersensitivity to this product or other products derived from NSO mammalian cells or any component of this product. **CIMAher™** (Nimotuzumab) should be used with caution in patients with chronic diseases in decompensate phase, such as cardiac dysfunction, diabetes mellitus or arterial hypertension or in patients with history of severe allergies 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, lack of EGFR can cause lack of maturation of the epithelium and postnatal death. EGFR has been implicated in the control of prenatal 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 from the mother to the developing fetus. 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 risks to the fetus. If the patient becomes pregnant while receiving this drug, she should be informed of the potential hazard to the fetus and/or 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 study. The repeated application of Nimotuzumab as monotherapy was well tolerated and safe. The clinical deteriorations were mostly associated with complications of the tumor disease, tumor progressions or, rarely, with another concomitant disease. In particular no allergic reactions or severe skin or gastrointestinal toxicity were observed. No safety concerns arose from laboratory tests, vital signs, or physical examination findings. No severe hematological or non-hematological side effects associated with the Nimotuzumab monoclonal antibody were seen. A phase III study of newly diagnosed diffuse intrinsic pontine glioma in pediatric/adolescent 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, pyrexia, tremors and vomiting. In the pediatric trial, non-serious adverse events considered at least possibly related to Nimotuzumab included erythema, fatigue, headache, leucopenia, nausea and vomiting. Rare adverse events reported were myalgia, somnolence, disorientation, hematuria, and elevated liver functions enzymes. In clinical experience, potentially fatal allergic reaction was very rarely reported. This event includes rapid and severe hypotension and urticaria.

**Drug interactions**

The interaction of Nimotuzumab with other cytostatic drugs has not been evaluated to date, although there does not appear to be any significant interaction with co-administered gemcitabine. An ongoing study in colorectal cancer in which Nimotuzumab is being administered with irinotecan has not demonstrated any untoward effects to date. Synergistic effects and potentiation of the anti-tumor activity had been already shown when other EGFR inhibitors have been used in combination with chemotherapy.

**Overdosage**

A phase I study conducted in Canada has demonstrated that doses up to 800 mg/week 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 discoloration prior to administration, if these are presents do not use the product.
3. Use a sterile syringe and appropriate aseptic technique. Remove the cap from the vial containing **CIMAher™** (Nimotuzumab) and clean the top of the vial with anti-bacterial solution, and insert the needle into the vial to extract the content.
4. The **CIMAher™** (Nimotuzumab) at the selected dosage should be diluted in 250 ml of sodium chloride 0.9%.

**Storage conditions**

1. **CIMAher™** (Nimotuzumab) should be stored in refrigerator at 2-8 °C. The biological activity of the antibody may be lost after freezing and thawing. Do not freeze or shake.
2. The antibody diluted in the saline buffer is physically and chemically stable for up to 72 hours when stored at room temperature (25 ± 3°C). Nimotuzumab diluted in 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 10 ml vial contains Nimotuzumab 5 mg/ml

Reg. No. R 2007AA2558

**ON MEDICAL PRESCRIPTION ONLY.**

Date of Revision of Package Insert : 19 November 2015

**Manufactured by:**
Center of Molecular Immunology (CIM)
Calle 216 esq. 15 Atabey, Playa C.
Havana, Republic of Cuba

INNOGENE KALBIOTECH

KALBE

Size : 95 x 300 mm

95 mm

95 mm

Keterangan :
1. Warna dasar : Putih
2. Leter, Logo Kalbe Logo Biotech : Hitam
3. Jenis kertas : HVS 60 g/m$^2$
4. Size : 95 x 300 mm
5. Lipatan : A1 - A2
6. Cetak : 2 (dua) Muka

***Kolom Persetujuan***

| Bagian | R & D | | | QA/QC | Marketing | | BD+Registrasi | | KGID** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Formulasi/Andev. | Packdev | Packdev | | | | | | | |
| Paraf | | | | | | | | | | |
| Nama | | | | | | | | | | |
| tanggal | | | | | | | | | | |
| Keputusan* | ok / tidak | ok / tidak | ok / tidak | ok / tidak | ok / tidak | ok / tidak | ok / tidak | ok / tidak | ok / tidak | ok / tidak |

* Beri tanda √
Jika masih ada revisi, berí tanda √ pada 'tidak' dan komentar langsung ditulis/ditambahkan pada fisik artwork
**KGID diisi jika produk eksport

**For internal purpose only**
*(ørl-1) 21.09.2010 str*
*(ørl-2) 24.09.2010 rev rdksi*