

## **CIMaHer<sup>®</sup>, (nimotuzumab) a humanized monoclonal antibody against epidermal growth factor receptor.**

### **Description:**

**CIMaHer (nimotuzumab)** is a humanized monoclonal antibody that recognizes the Epidermal Growth Factor Receptor (EGF-R) with high affinity.

The antibody was obtained by cloning the variable regions of the murine antibody **ior egf/r3** into human immunoglobulin framework (Eu for heavy chain and REI for light chain). Is an **IgG<sub>1</sub>** antibody and has a molecular weight of 150 KD.

**CIMaHer** is produced through mammalian cell culture of non-secreting NSO cells.

### **Pharmaceutical composition:**

**CIMaHer** is formulated as a colorless sterile solution in 10 mL of buffer saline.

Each vial contains 50 mg of **CIMaHer**, 4.5 mg of Sodium Phosphate Monobasic (NaH<sub>2</sub>PO<sub>4</sub>), 18.0 mg Sodium Phosphate Dibasic (Na<sub>2</sub>HPO<sub>4</sub>), 86.0 mg of Sodium Chloride, 2.0 mg of polysorbate 80 and water for injection in the amount to complete 10 ml.

### **Pharmacological Properties:**

The EGF-R is a transmembrane glycoprotein of 170 KDa. Its intra-cellular domain is associated with specific tyrosine kinase activity and its over-expression on the cancer cells alters the cell cycle regulation (increasing proliferation), block apoptosis, promote angiogenesis, increase motility, cell invasion and metastasis.

**CIMaHer** blocks the binding of the EGF to its receptor and inhibits in vivo and in vitro tumor cell and has a potent antiangiogenic effect, anti-proliferative and pro-apoptotic in those tumors that over-express the EGF-R.

### **Pharmacological Actions.**

#### **Patients with advanced head and neck tumors:**

In patients with stage III and IV tumor lesions the oncospecific treatments consist in radiotherapy and chemoradiotherapy. The percent of objective responses (complete and partial remissions) to radiotherapy and chemoradiotherapy in these stages is 30-40 % and 50-60% respectively. The use of **CIMaHer** in combination with radiotherapy and chemoradiotherapy increase the percent of objective response to as much as 70 -80%. Survival mean and median were 24.19 months and 15 months in patients treated with CIMaHer while the survival mean and median for the patients treated with placebo were 14.12 and 9.27 months respectively (p= 0.024).

#### **Pediatric patients with recurrent/refractory high grade malignant astrocytoma**

In pediatric patients with high grade malignant astrocytoma recurrent or refractory to surgery, radiotherapy and chemotherapy, none of the previously and currently used chemotherapy protocols is recommended as treatment.

In pediatric patients treated with **CIMaHer** as monotherapy, the antitumor response was 37.8%. The survival median was 8.9 months for the responders patients compared with 3.3 months for non responders (p ≤ 0.05).

#### **Adult patients with Glioblastoma multiforme**

In Glioblastoma multiforme patients, treated with **CIMaHer** plus with radiotherapy, the survival median was 16.3 months compared with the expected 12 months for radiotherapy alone.

No severe adverse events were observed with **CIMaHer** treatment.

#### **Indications.**

##### **Patients with advanced head and neck tumors**

**CIMaHer** is indicated for use in the treatment of advanced Squamous Cell Carcinoma of Head and Neck region with concurrent chemotherapy and / or radiotherapy.

##### **Pediatric patients with recurrent/refractory high grade malignant astrocytoma**

**CIMaHer** is indicated, as monotherapy, for use in the treatment of high grade malignant astrocytoma recurrent/refractory to surgery, radiotherapy and chemotherapy in pediatric patients.

#### **Adult patients with Glioblastoma multiforme**

**CIMaHer** is indicated for use in the treatment of adult patients with Glioblastoma multiforme, with concurrent radiotherapy.

#### **Contraindications:**

Has not been reported so far until today.

#### **Precautions:**

**CIMaHer** should be administered with cautions in patients who have previously received treatment with the murine monoclonal antibody **ior egf/r3**, patients with previous hypersensitivity to this product or other product derived from NSO mammalian cells or any component of this product. **CIMaHer** should be use with cautions in patients with chronic diseases in uncontrolled phase, for example: Cardiac dysfunction, diabetes mellitus or hypertension arterial.

#### **Use in pregnancy and lactation**

It is unknown the effect of **CIMaHer** in pregnancy. Animal studies have shown that at the embryonic stage, lack of EGF-R can cause not maturation of the epithelium and postnatal death. The use of **CIMaHer** during pregnancy stage it is not recommended and it is not known if **CIMaHer** is secreted on human milk it is not recommended its use in lactating women.

#### **Adverse Reactions**

The principal adverse reactions that could appear after the administration of **CIMaHer** consist on mild or moderate reactions like tremors, chills, nauseas, vomiting, anemia, hypotension or hypertension

Other reactions but less frequently that could appear consist on somnolence, disorientation, myalgia, motor dysfasia, dried mouth, flushing, weakness in the lower limbs, raising creatinine levels, leukopenia, haemoglobinpenia, chest pain and cyanosis of the mouth.

These adverse reactions respond to the treatment with analgesics and anti-histaminic at conventional dosage.

### Interactions and incompatibilities

The interactions of CIMAher with other cytostatic drugs have not been totally evaluated so far until today. Had been already shown a synergistic effect and potentiation of the anti-tumor activity when other EGF-R Inhibitors have been used in combination with chemotherapy.

### Dosage.

#### Patients with advanced head and neck tumors:

The recommended dosage of **CIMAher** is 200 or 400 mg, administered once a week during six weeks, in combination with a standard radiotherapy and / or chemotherapy for head and neck cancers.

During the consolidation period, the recommended dose is 200 or 400 mg, every 15 days until progression of clinical deterioration.

#### Pediatric patients with recurrent/refractory high grade malignant astrocytoma

The recommended dosage of **CIMAher** is 150 mg/m<sup>2</sup>, administered once a week during six weeks as monotherapy.

During the consolidation period, the recommended dose is 150 mg/m<sup>2</sup>, every 15 days until progression of clinical deterioration.

#### Adult patients with Glioblastoma multiforme

The recommended dosage of **CIMAher** is 200 mg, administered once a week during six weeks, in combination with a standard radiotherapy.

During the consolidation period, the recommended dose is 200 mg, every 15 days until progression of clinical deterioration.

In all Indications, **CIMAher** will be administered as continuous intravenous (IV) infusions and the antibody is diluted in 250 ml of sodium chloride and infused over 30 minutes.

#### Duration of the therapy:

The treatment with **CIMAher** will have two stages, induction and consolidation, in all indications.

The induction period will be done once a week until the administration of six doses is completed, concurrent with the recommended radiotherapy or chemoradiotherapy, according the indication. Temporally discontinuation of the **CIMAher** treatment will be done when the radiotherapy or chemoradiotherapy is interrupted. Once the radiotherapy / chemoradiotherapy start, the administration of **CIMAher** continues.

The consolidation period, **CIMAher** will be administered every 15 days until progression of clinical deterioration.

#### Over dosage:

The effects of over dosage of **CIMAher** are not known so far until today.

### Preparation for administration

1. Do not shake the content of the vial. A vigorous shaking could denaturalize the protein and affect the biological activity of the product.
2. Any product that is supposed to be administered by parenteral infusion should be inspected visually for particulates and discoloration prior to administration.
3. Using appropriate aseptic techniques, proceed using sterile syringe. Take of the flip off of the vial that contains **CIMAher** and clean the top of the vial with anti-bacteriostatic solution and insert the needle in the vial to extract the content.
4. The **CIMAher**, at the selected dosage should be diluted in 250 ml of sodium chloride 0.9%.

### Storage conditions:

**CIMAher** should be stored refrigerated at 2 - 8 °C. Do not frost or shake.

### Presentation

Each vial contains 50 mg of CIMAher, at a concentration of 5 mg/mL, in a total volume of 10 mL of saline buffer.



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