CECMED
CENTRO PARA EL CONTROL ESTATAL DE MEDICAMENTOS, EQUIPOS Y DISPOSITIVOS MÉDICOS
Ministerio de Salud Pública de Cuba

SUMMARY OF THE CHARACTERISTICS OF THE PRODUCT

Name of the producer: CIMAher®
(Nimotuzumab)

Pharmaceutical form: IV Injection

Strength: 5 mg/mL.

Presentation: Case with 4 vials of 10 mL each.

Titular of the Sanitary Registration, country: Centro de Inmunología Molecular, Cuba.

Manufacturer, country: 1. Centro de Inmunología Molecular, Cuba.

- Planta de Producción de Anticuerpos Terapéuticos (ANTYTER). *Active Pharmaceutical Ingredient*
- Plant 3.
  Formulation, filling and packing.

2. Biotech Pharmaceutical. Co. Ltd., China.

- API manufacturing plant.
  Active Pharmaceutical Ingredient

Sanitary Registration Number: 1745.

Registration date: February 19, 2002.

Composition: Each vial contains:

Substance	**Quantity**
Nimotuzumab	50, 0 mg
Dibasic sodium phosphate	
Monobasic sodium phosphate	
Sodium chloride	
Polysorbate 80	
Water for injection csp	

Validity term: 36 months.

Storage conditions: Temperature between 2 and 8 □C. Protect from light. Do not freeze, do not stir.

Therapeutic indications:

- Treatment of head & neck tumors in advanced stages in combination with radiotherapy and & or chemotherapy.
- Treatment of adult patients with high-malignant glial tumors:
  Multiform Glioblastoma and **Anaplastic astrocytoma,** in combination with radiotherapy.
- **Treatment of pediatric patients with newly diagnosed high-malignant glial tumors with radiotherapy and chemotherapy**.

- Treatment of pediatric patients with recurrent or refractory glial tumors with nimotuzumab.
- Treatment of patients carrying non-resectable esophagus malign tumors of epithelial origin in combination with radio-chemotherapy.
- **Treatment of patients carrying locally advanced or metastatic pancreas adenocarcinoma, in combination with chemotherapy.**

Contraindications:

Patients presenting antecedents of hypersensitivity to this or other product derived from superior cells or other component of this product's formulation.

Precautions:

CIMAher® should be administered with precaution in patients who have received previous treatment with the murine monoclonal antibody ior® egf/r3. CIMAher® should be used with precaution in patients carrying chronic illnesses in a destabilized phase, for example: ischemic heart disease, diabetes mellitus or arterial hypertension. Usage not recommended during pregnancy or nursing.

Special warning and precautions for use:

CIMAher® does not contain any preserving agent in its formulation, therefore, CIMAher® should be used immediately after opening the vial for preparing the infusion.

CIMAher® diluted into a saline infusion at 0.9% is physically and chemically stable for 72 hours, at a temperature not exceeding 27ºC. If the limit is exceeded, the infusion must be thrown away.

Undesirable effects:

The main adverse reactions that could appear after administering CIMAher® consist in light to moderate reactions such as tremors, chills, nauseas, headache, vomits, anemia, arterial hypotension or hypertension, fever and increase of the alkaline phosphatase, TGP and TGO.

Other less frequent reactions that could appear consist in somnolence, disorientation, myalgia, motor dysphasia, incoherent speech, mouth dryness, facial blushing, lower limbs' weakness, phlebitis, creatinine increase, leucopenia, hematuria, thoracic pain and peri-buccal cyanosis.

These adverse reactions respond to treatment with analgesics and antihistamines in conventional doses.

Posology and way of administration:

- *Advanced head and neck tumors:*

The recommended dose of CIMAher® is 200 mg, administered once a week for 6 weeks, concomitant with radiotherapy and/or chemo-radiotherapy. Afterwards, a dose of 200 mg will be administered every 15 days (maintenance dose) while the patient's general condition permits.

- *Recurrent and newly diagnosed high-malignant pediatric astrocytoma:*

The recommended dose of CIMAher® is 150 mg/m^2, administered once a week for 6 weeks as mono-therapy. Afterwards, a dose of 150 mg/m^2 will be administered every 15 days (maintenance dose) while the patient's general condition permits.

- *Multiform glioblastoma and anaplastic astrocytoma in adults:*

The recommended dose of CIMAher® is 200 mg, administered once a week for 6 weeks, concomitant with radiotherapy. Afterwards, a dose of 200 mg will be administered every 15 days (maintenance dose) while the patient's general condition permits.

Malign non-resectable esophagus tumors of epithelial origin in combination with radio chemotherapy:

The recommended dose of CIMAher® is 200 mg, administered once a week for 6 weeks, concomitant with radiotherapy. Afterwards, a dose of 200 mg will be administered every 15 days (maintenance dose) while the patient's general condition permits.

- *Locally advanced or metastatic pancreas adenocarcinoma in combination with chemotherapy.*

The recommended dose of CIMAher® is 400 mg administered once a week, in combination with chemotherapy. CIMAher® will be administered until progression disease or non-acceptable toxicity.

For all clinical indications, CIMAher® shall be administered by intravenous way in 250 mL saline solution in quick infusion (30 minutes).

Interactions with other drug products and other forms of interaction

CIMAher® interaction with other cytostatic drugs is currently subject to an evaluation phase. It has been proved synergism or leverage of the antitumor activity when the agents inhibiting the EGFR have been used in combination with radiotherapy.

Use in pregnancy and nursery:

The usage of CIMAher® during pregnancy and nursery is not recommended.

Effects on vehicle and/or machinery conduction:

CIMAher® effects on vehicle/machinery conduction is unknown.

Overdose:

Effects of CIMAher® overdose are unknown.

Pharmacodynamic properties:

CIMAher® is a humanized antibody recognizing with high affinity the epidermal growth factor (EGF-R).

The EGF-R is a 170 Kd membrane glycoprotein. Its intracellular domain is associated to the specific tyrosine kinase protein, and its over-expression by the tumor cells alters the regulation of the cellular cycle (increasing proliferation); it blocks apoptosis, promotes angiogenesis, increases motility, adhesiveness and invasive capability.

CIMAher® blocks the ligand's union to the EGF-R and functions by inhibiting the tyrosine kinase activity of the receptor, interfering with the cellular signalization route involved in the cellular proliferation. CIMAher® has an anti-angiogenesis, anti-proliferative and pro-apoptotic effect, in those tumors over-expressing the EGF-R; it, therefore, inhibits the growth *in vitro* and *in vivo* of epithelial origin tumor cells.

PHARMACOLOGICAL ACTIONS

Patients with head and neck tumors in advanced stages:

In patients carrying tumor lesions, stages III and IV, the oncospecific treatment consists in radiotherapy or chemo-radiotherapy. The objective response percentage (complete and partial remissions) to the standard therapy is 30-40 % and 50-60% respectively. CIMAher® concomitant use with radiotherapy and/or chemo-radiotherapy increases the percentage of objective response to values between 70 (radiotherapy and nimotuzumab) and 100% (chemo-radiotherapy and nimotuzumab), while the global survival rate of the patients treated with the combination nimotuzumab and chemo-radiotherapy is 70% after 30 months of monitoring.

Pediatric patients with high-malignant recurrent and/or refractory astrocytoma:

In patients carrying recurrent brain tumors, refractory to surgery, to irradiation and to therapy with cytostatic agents, life expectancy is approximately one month. The survival median for this type of pediatric patients who received monotherapy with CIMAher® at a dose of 150 mg/m2 is of 8.9 months. Control and stabilization of the illness is noteworthy for this group of patients.

Pediatric patients with newly diagnosed high grade malignant glial tumors in combination with radiotherapy and radio-chemotherapy

In pediatric patients with newly diagnosed brain-stem diffuse glioma, evaluation took place of a combination of nimotuzumab with radiotherapy and vinorelbine (20 mg/m2). The primary objective of the study was the response rate, which was observed in 96 % of patients. Combination was very well tolerated without acute adverse events. Eleven from sixteen patients presented local relapse and were re-irradiated. The progression-free survival and global survival rate were of 8.5 and 15 months respectively. The progression-free survival rate in re-irradiated patients (11) was of 8.3 months in comparison with 8.5 months of the remaining included patients (14). The survival median for this re-irradiated-in-relapse group was of 13.3 months, while for those non-irradiated-in-relapse patients it was 12 months (p= 0.03).

Adult patients with multiform glioblastoma and anaplastic astrocytoma:

In patients with high malignant astrocytic tumors, expected survival with radiant therapy alone corresponds to 12 months for tumors classified as multiform glioblastoma, and 24 months for the astrocytomas grade III or anaplastic. In patients carrying multiform glioblastoma, treated with **CIMAher®** combined with radiotherapy, the median and mean survival values were of 16.30 and 20.45 months respectively. For patients with anaplastic astrocytoma who received the combination, the survival mean reached is 30.03 months.
In a post commercial study it was observed that the progression-free survival median and the survival median by intention to treat for this type of patients was of 8.6 months and 12.23 months respectively. According to the histological grade, for patients with glioblastoma, the survival median was 10.56 months and for patients with anaplastic astrocytoma it was of 28.26 months. The 24 months survival rate was 21.6 % and 57.1 % respectively.

Patients with non-resectable, malign esophagus tumors of epithelial origin in combination with radio-chemotherapy

In patients with malign esophagus tumors, receiving standard therapy, expected survival is three months, while in patients treated with CIMAher® in combination with radio and chemotherapy the survival median obtained is 8, 1 months. The clinical control of the illness is obtained in 60.9% of patients treated with CIMAher® plus chemo-radiotherapy, while in patients receiving chemotherapy alone it reaches 26,9 %. CIMAher® combined with chemo-radiotherapy does not increase the appearance of serious adverse events in comparison with the standard treatment.

Patients with locally advanced or metastatic pancreas adenocarcinomas in combination with chemotherapy

Patients with locally advanced or metastatic pancreas adenocarcinomas showed an increase in survival time after a combined treatment with nimotuzumab and gemcitabine. The global survival median increased from 6, 0 months in the control group (gemcitabine plus placebo) to 8, 6 months in the research group (nimotuzumab plus gemcitabine). Survival rate at one year also was higher for patients who received nimotuzumab and gemcitabine compared to the control group (34, 4% vs. 19, 2%). Patients carrying tumors with the non-muted KRAS oncogene showed a higher increase of the survival time. Survival media increased from 5, 7 months in the gemcitabine/placebo group to 11, 6 months in the group treated with nimotuzumab and gemcitabine.

Patients treated with nimotuzumab and gemcitabine showed also a significant increase in the progression-free survival (4, 47 months) in comparison to the group treated with gemcitabine and placebo (3, 23 months).

Pharmacokinetic properties (absorption, distribution, biotransformation, elimination):

Pharmacokinetic data show CIMAher® presenting a non-linear pharmacokinetic behavior between doses of 50 and 200 mg. The higher the product's values, the higher the increase in the average time for its distribution, elimination and of the distribution volume.

The pharmacokinetic analysis in patients who had received CIMAher® infusions between 50 and 400 mg, demonstrated that the average time for elimination correspond to 62.91 ± 61.81 hours, 82.6 ±7.89, 302.94 ± 44.13, 304.51 ± 50.7 hours for doses of 50, 100, 200 y 400 mg, respectively. The average time for elimination increased linearly with the dose up to the 200 mg dose. The clearance values reported for CIMAher® were 1.22 ± 0.46 mL/min, 0.69 ± 0.08 mL/min, 0.41 ± 0.17 mL/min and 0.74 ± 0.40 mL/min the four doses studied, respectively.

Liver, heat, spleen, kidneys and urinary bladder, were identified as target organs, observing significant incorporation in liver and light to moderate incorporation in other organs.

Instructions for the use, handling and destruction of the non-usable product's remainder:

WAY OF PREPARATION

1. Verify the vials to be within the validity period declared on the label and that the product has been stored at a temperature from 2 to 8 °C.
2. Place a sterile needle onto a sterile syringe
3. Remove the flip *off* cover from the vial containing CIMAher® and clean its upper part with a disinfectant.
4. Insert the needle into the rubber tampon and extract the content of the vial.
5. Inoculate the content of the four vials into 250 mL sodium chloride solution at 0.9 %.
6. Administer intravenously (antecubital vein) the saline solution as a quick injection (30 minutes).

Date of approval / revision of the text: August 10, 2015