℞ NIMOTUZUMAB

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BIOMAb EGFR®

Description

Nimotuzumab is a recombinant humanized monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR) by interacting with epitope located in the extra cellular domain of this receptor. Nimotuzumab is a humanized form of murine lgG2a monoclonal antibody R3 (ior egf/r3). The humanized Nimotuzumab lgG1 antibody is obtained by cloning the CDRs of the murine antibody into human Frs (Eu for heavy chain and REI for light chain) and the reintroduction of 3 murine residues into human Frs of heavy chain.

Composition:

Each 10 ml vial contains	
Nimotuzumab	50.0 mg
(Humanized anti-EGFR monoclonal antibody)	
Sodium phosphate dibasic	18.0 mg
Sodium phosphate monobasic	4.5 mg
Sodium chloride	86.0 mg
Polysorbate 80	2.0 mg
Water for injection	qs 10 mL

The product is formulated as a colorless and clear solution, without insoluble matters.

Clinical Pharmacology

Nimotuzumab binds to the extracellular domain of epidermal growth factor receptor (EGFR, HER1, c-ErB1) and inhibits the binding of epidermal growth factor (EGF) and other ligands such as transforming growth factor alfa. The intrinsic properties of Nimotuzumab require bivalent binding (i.e., binding with both antibody arms to two targets simultaneously) for stable attachment to cellular surface, which leads to Nimotuzumab selectively binding to cells that express moderate to high EGFR levels1. The EGFR is a transmembrane glycoprotein that is a member of a family of receptors named HER. 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). In wide diversity of human tumors of epithelial origin like head and neck (SCCHN), non small cell lung cancer (NSCLC), pancreatic, colon, breast, kidney ovarian and bladder carcinomas EGFR is over expressed. It is also over expressed in gliomas. Binding of Nimotuzumab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased vascular endothelial growth factor production.

In vitro studies using tumor cell lines like A431, MDA-MB-435, U87 and in vivo studies in human tumor xenografted SCID mice have shown that Nimotuzumab has anti-proliferative, anti-angiogenic and proapoptotic activity.

Human 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. Nimotuzumab clearance (CL) decreased from 1.08 to 0.34 mL/h/kg as the dose increased from 50 to 200, and at doses >200 mg, it appeared to plateau. The volume of the central compartment (Vc) for Nimotuzumab ranged from 2.3 to 7.2L and the maximal concentration Cmax was 27 to 57 ng/mL for the same dose range. The elimination half life (t 1/2ß) ranged from 62.91 to 304.51 hrs for the doses 50 to 400mg.

In the human body, Nimotuzumab is mainly distributed in liver, spleen, heart, kidney and bladder. Liver uptakes most of the Nimotuzumab. Evidence from animal pharmacokinetic study indicates that the concentration of the antibody in tumor is highest at 24 hours after injection.

Clinical Studies

The efficacy and safety of Nimotuzumab concurrently with chemotherapy and / or radiotherapy has been studied in two randomized controlled trials (RCT) (229 patients) and two non randomized (53 patients) clinical trials. Safety data from all of these patients were also evaluated.

Randomized, Controlled Trials

A randomized multicentric phase II clinical trial enrolled 92 patients to study the addition of Nimotuzumab to two regimens of standard of care namely Radiotherapy (RT) and Chemotherapy (CT) + RT in the management of stage III & stage IVA unresectable head and neck cancer. The two groups were evenly matched with respect to the age, sex, stage of tumor and baseline KPS with no statistical difference between the groups. Patients received Nimotuzumab as 200 mg IV infusion weekly once for 6 weeks. The response to treatment was evaluated at the end of 3 months and 6 months. A total of sixteen patients were not evaluable. 76 patients were evaluable for efficacy analysis.

The objective response rates (ORR) in the different treatment groups were:

Treatment groups	n =54#	ORR % (p value)
Nimotuzumab +RT	**13**	**76.47* (0.02)**
RT	**7**	**36.84**
Nimotuzumab +CT+RT	**20**	**100.00♦(0.02)**
CT+RT	**14**	**70.00**

* **Nimotuzumab + RT vs RT**
♦ **Nimotuzumab +CT+ RT vs CT+RT**
54 patients showed ORR of the 76 evaluable for analysis

Nimotuzumab did not deteriorate the KPS of the patient when it was added to CT+RT and RT. Nimotuzumab when used concurrently with CT and / or RT showed greater Objective Response Rate than the control treatment groups. At 30 months follow up2, the survival rate in Nimotuzumab plus Chemoradiation arm was 69.5% versus 21.7% in chemoradiation alone arm and in Nimotuzumab plus radiotherapy arm was 39.1% versus 21.7% in radiotherapy alone arm. The addition of Nimotuzumab to Chemoradiation resulted in a reduction in risk of death (rrd) by 85 % (HR 0.15, p-0.0006) and to RT a 36 % rrd (HR0.64, p 0.33) (OS per protocol).

In another randomized, open-labeled multi-centric phase II clinical trial in patients with locally advanced (stage III or IVA-B) nasopharyngeal squamous carcinoma3 137 patients were included out of which 70 were in the study drug (Nimotuzumab) group, and 67 in the control group. Patients in the study drug group received Nimotuzumab in combination with radical radiotherapy, while the control group received radiotherapy alone. Patients received 8 weekly infusions of Nimotuzumab at the dose of 100 mg in combination with radiotherapy. The first infusion was given on the same day patients started radiotherapy and ended simultaneously with the radiotherapy.

Analysis was performed at the end of the treatment, 5 and 17 weeks after the treatment separately. Upon the end of the treatment, the CR (Complete Remission) percentage of study drug group was: 76.56% for primary tumor, 75.00% for lymph node, and 65.63% for overall evaluation; compared with those of control group as 34.85%, 57.58%, and 27.27% respectively. The CR percentages in study drug group were higher than those in control. 5 weeks after the treatment, the CR percentages in study drug group were 90.63% for local tumor, 89.06% for lymph node, and 87.50% for overall evaluation; compared with the control group of 51.52%, 72.73%, and 42.42% respectively. 17 weeks after the treatment, the CR percentages in study drug group were 92.19% for local tumor, 93.75% for lymph node, and 90.63% for overall evaluation, compared with 63.64%, 80.30%, and 51.52% in the control. All differences were statistically significant. The objective response observed at 17 weeks after the treatment was 100% in study drug group and 90.91% in control group. The difference was statistically significant. The mean value of Karnofsky grading of study drug group after treatment was higher than that of control group, which was statistically significant, which indicates that the antibody is helpful to improve the patient life quality. The differences between the patient body weights before and after the treatment were analyzed and the mean value of experimental group was 0.35 kg and that of control group was 0.87 kg and this difference was statistically significant.

Non-Randomized Trials

A single center phase I / II open-label, nonrandomized, clinical trial was designed to evaluate safety, and efficacy of Nimotuzumab in combination with external beam radiotherapy in 12 advanced EGF-R expressing head and neck cancer (Stages III or IV) patients suitable for radical radiation therapy. Four different treatment cohorts of 3 patients were established. Single doses in the 4 defined cohorts from 50 to 400 mg of Nimotuzumab. Patients received the same dose on a weekly basis for 6 weeks. For the 4 cohorts, total Nimotuzumab cumulative doses were 300, 600, 1200, and 2400 mg. Patients also received either 60 or 66 Gy radiation depending on response from Co 60 sources at 2Gy doses given daily for five days over six weeks. After finishing accrual, the protocol was amended to include five new patients in the two highest dose groups to further evaluate the relationship between the antitumor response and serum antibody levels.

In the first trial section, where 12 patients took the 4 dose levels of Nimotuzumab, 7 patients of the 12 showed ORR (PR or CR), and four subjects showed stable disease and there was tumor progression in 1 case after the combined therapy. In 6 of the 7 responding patients, there was complete remission of the primary tumor and its metastases while 1 patient showed a partial response. Preliminary pharmacokinetic analysis indicated that receptor saturation was achieved above 200 mg.

Overall survival significantly increased after the use of doses of 200 or 400 mg in comparison with lower doses (P=0.03). With a median follow-up from treatment beginning to the closeout date of 45.2 months (range, 41.5 to 48.1months), the median survival for 50 and 100 mg treated patients was 8.60 months, while the median survival of the patients receiving 200 and 400 mg was 44.30 months. The 3-year survival rate was 16.7% for subjects treated with the two lowest doses and 66.7% for the patients treated with 200 and 400 mg. After the protocol was amended to include 10 new patients in 200 and 400 mg groups, finally, 14 (87.5%) of the 16 patients achieved ORR where 11 were CR. The overall mean survival is 22 months; 8 patients remain alive and seven are disease free4.

Another multi-centric nonrandomized study evaluating the safety and efficacy of Nimotuzumab in combination with radiation therapy (RT) in the treatment of patients with locally advanced, unresectable squamous cell carcinoma of the head and neck (SCCHN) was conducted in thirty one subjects. Patients were treated with radiotherapy of 6600 or 7000 cGy in 33 or 35 fractions plus 100 or 200 mg doses of Nimotuzumab once weekly for 6 weeks. The ITT population was defined as all patients who received at least one dose of Nimotuzumab. The evaluable population was defined as all patients who received six doses of Nimotuzumab and reached week 12 evaluations Twenty-four patients were fully evaluable. Of these, 17 (70%) showed complete tumor responses as their best response. In total, thirteen patients completed the study as complete responders. Of the remaining evaluable patients, 3 (12.5%) patients achieved partial responses and then progressed at 24 week, 1(4.9%) patient had stable disease for 3 visits and then progressed. The remaining 3 (12.5%) patients had progressive disease. The mean survival in the ITT population was 829 days. The median survival of the evaluable population is currently 43.4 months.

Indication

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

Dosage and Administration Method

Nimotuzumab is administered as continuous intravenous (IV) infusions in weekly doses of 200 mg for 6 weeks, in combination with a standard radiotherapy and / or chemotherapy for head and neck cancers. 200 mg of the antibody is diluted in 250 ml of sodium chloride and infused over 60 minutes.

During dilution with normal saline ensure that all precautions are taken to avoid accidental contamination. In case of any turbidity being seen in the solution it is due to accidental microbial contamination. In such case please discard the solution and prepare a fresh solution.

Adverse Reactions

In a randomized clinical trial in patients with head and neck cancers where Nimotuzumab was used concurrently with or without RT and/or CT, the commonly reported adverse events in the radiotherapy group were fever,

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chills, mucositis, pruritis, urticaria/rash, headache, hypertension and fluctuation in blood pressure. The reported adverse events in the chemo radiotherapy group were mucositis, asthenia, dizziness, haematuria (microscopic), vomiting and loose stools. Only rash and chills was rated by the investigator as certainly related to Nimotuzumab. These adverse events were mild to moderate in severity, self-limiting reversible and probably or possibly related to Nimotuzumab. Three patients showed first dose infusion reaction and recovered without any sequelae and were able to withstand subsequent infusions of Nimotuzumab. One patient had a serious anaphylactic reaction with skin rash that was treated with symptomatic therapy and was withdrawn from the study.

In the chemo radiotherapy group the proportion of patients reporting grade III & IV adverse events in the Nimotuzumab arm was more than the arm without Nimotuzumab. These adverse events were related mostly to the concurrent CT+RT rather than to Nimotuzumab. The radiotherapy group showed proportion of patients with grade III & IV adverse events to be more in the arm without Nimotuzumab in relation to RT than the Nimotuzumab arm. Addition of Nimotuzumab has not shown to potentiate the toxic effects of RT.

The anaphylactic skin reaction was the only SAEs reported due to the Nimotuzumab. The other SAEs reported were due to the underlying malignant disorder or as a result of treatment with concurrent chemotherapy or radiotherapy.

In the clinical trial on advanced nasopharyngeal squamous carcinoma the most frequently observed adverse reaction include low fever, hypotension, nausea, dizziness and skin rash. Among the 70 patients of the experimental group treated with the drug, the incidence of Grade I fever, , was 4.28%, and the highest temperature was 39 oC, which decreased after treatment and did not interrupt the therapy schedule; the incidence of hypotension and dizziness was 2.86%, and the lowest blood pressure recorded was 80/50, which normalized after rest. The incidence of Grade I nausea and skin rash, was 1.43%.

Adverse reactions observed in clinical trials when Nimotuzumab was used along with radiotherapy for the treatment of advanced epidermal derived tumors in head and neck cancers were classified as common and rare reactions, and are listed in Table1. Most of the adverse reactions related to the drug, were of Grade I and II severity. No skin rash or other skin toxicity was reported.

Table 1 Incidence of common adverse reactions in patients with advanced epidermal derived cancers

Adverse reaction	Incidence% Grade I	Incidence% Grade II	Incidence% Grade III
Fever	14.2	2.6	16.8
Tremors	11.6	5.2	16.8
Nausea and vomiting	10.9	2.6	13.5
Chills	12.2	1.3	13.5
Hypotension	5.2	2.6	7.8
Weakness	7.8	0.0	7.8
Headache	5.6	0.0	5.6
Anaemia	4.3	1.3	5.6
Acral Cyanosis	3.0	2.6	5.6

In a single arm non randomized clinical trial one patient developed a grade 3 somnolence after his first dose. Other mild or moderate reactions were fever, vomiting, nausea, hypotension, tremors, chills, headache, disorientation, precordial pain, dysphasia and myalgias. These adverse events were controlled by standard medication. Irradiation toxicity was not exacerbated by the addition of Nimotuzumab to standard radiotherapy.

In the second non randomized study in SCCHN patients the most common radiation associated adverse events were taste alteration, dysphagia, stomatitis, mucositis, and pain in the throat and erythema in the radiation field. None of these were unexpected and there did not appear to be any exacerbation associated with administration of the antibody. Nausea and fatigue were the most commonly reported non-radiation associated adverse event. Infusion reactions occurred only in four patients receiving a single specific lot of Nimotuzumab. There were 13 SAEs reported. The serious adverse events reported were mainly due to disease progression or metastatic disease and were deemed not related to study therapy. This included two deaths; one patient died following hemorrhage from the esophageal component of his tumor and a second patient died due to unknown cause.

Precautions

BIOMab EGFRTM should be used with caution in patients with known hypersensitivity to Nimotuzumab or to any of the known components of the formulation. (See DESCRIPTION for other components in the formulation)

Contraindication

None known.

Drug Interactions

The effect of concomitant administration of other drugs on Nimotuzumab and the reverse has not been evaluated.

Immunogenicity

The immunotoxicity studies in green monkeys consisting of four intra-dermal doses of adjuvanted- Nimotuzumab elicited only sub maximal immunogenic response, suggestive of lesser immunogenecity with nonadjuvanted-Nimotuzumab.

Immunogenicity [human anti-human antibody (HAHA)] to determine the anti-idiotypic response against Nimotuzumab was evaluated in clinical studies at single and multiple doses to a maximum of 2400mg with a follow-up of one year. Out of the 34 patients evaluated only one patient showed a response. The low anti-idiotypic response is indicative of the humanized nature of the antibody and may also be responsible for the low hypersensitivity reaction. The development of an immunogenic response is dependent on a number of factors like timing of sample collection, sample handling, time of collection, underlying disease and concomitant medication. The incidence of development of antibodies to Nimotuzumab is not conclusive.

Use in pregnancy and lactation

Use in Pregnancy

Animal reproduction studies have not been conducted with Nimotuzumab. However, the 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. But it is not known whether the antibody can cause fetal harm when administered to a pregnant woman. 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/or the potential risk for loss of the pregnancy.

Use in Lactation

It is not known whether the antibody is secreted in human milk. Since human IgG1 is secreted in human milk, the potential for absorption and harm to the infant after ingestion is unknown. No recommendation is made on the potential benefit versus risk of administering Nimotuzumab to nursing mothers.

Pediatric Use

Clinical studies are currently ongoing in pediatric patients with neurological tumors without significant adverse events related to

Nimotuzumab.

Efficacy in heavily pretreated relapse high grade gliomas in children and adolescents has been demonstrated in a Phase II study. The repeated application of Nimotuzumab as monotherapy was well tolerated and safe. None of the SAEs was considered related to study medication. 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 antibody were seen, minimizing the risk of severe infections, blood transfusions and hospitalizations.

Geriatric Use

The maximum age limit evaluated in head and neck cancer clinical studies was 78 years. Clinical studies conducted with Nimotuzumab are not adequate to show any differences in response due to the effect of advanced age.

Over dosage

It has been demonstrated in completed clinical trials the dosage upto 400 mg are safe to humans. No conclusion is available now about the safety for doses above 400 mg.

Packaging

Available as single carton of 4 vials and each vial of 10mL (50 mg of Nimotuzumab).

Stability and Storage

BIOMab EGFRTM (Nimotuzumab) should be stored in a refrigerator at temperature between 2°C and 8°C. Do not freeze. Freezing and thawing will destroy the biological activity of Nimotuzumab.
Nimotuzumab diluted in sodium chloride solution is physically and chemically stable for 12 hours under 2~8 oC, and for 6 hours at room temperature (25 ± 3°C). Nimotuzumab may not be active in the prepared solution beyond these conditions, the solution should be discarded and fresh solution prepared for infusion.

Shelf life

24 months.

References

1. AACR Cancer Clinical Trials and personalized medicine 2008. Abstract # A36
2. ASCO Annual Meeting 2009. Abstract # 6041.
3. Biocon Ltd. Data on file.
4. Tania Crombet et al. J clin Oncol vol 22: 2004

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