



European Medicines Agency  
*Pre-authorisation Evaluation of Medicines for Human Use*

London, 06 March 2009  
Doc. Ref: EMEA/67305/2009

**WITHDRAWAL ASSESSMENT REPORT  
FOR  
THERALOC**

International Nonproprietary Name:  
**nimotuzumab**

**Procedure No. EMEA/H/C/931**

Day 180 Assessment Report as adopted by the CHMP with  
all information of a commercially confidential nature deleted.

This should be read in conjunction with the “Question and Answer” document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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## LIST OF ABBREVIATIONS

AE	Adverse event
AUC	Area Under the Plasma Concentration-Time Curve
CI	Confidence Interval
C <sub>max</sub>	Maximum Plasma Concentration
CR	Complete remission
CT	Chemotherapy
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Agency for the evaluation of medicinal products
ErbB1	Epidermal growth factor receptor (Syn)
GCP	Good Clinical Practice
h	Hour(s)
HAHA	Human anti-human antibodies
HAMA	Human anti-mouse antibodies
ITT	Intent-to-treat
K <sub>d</sub>	Dissociation constant
μM	Micromolar
μg	Microgram
mg	Milligram
ml	Millilitre
mAb	Monoclonal antibody
NSCLC	non-small cell lung cancer
PD	Progressive disease
PK	Pharmacokinetics
PP	Per protocol population
RECIST	Response evaluation criteria in solid tumours
RT	Radiotherapy
SCCHN	Squamous cell cancer of the head and neck
SAE	Serious adverse event
SD	Stable disease
SmPC	Summary of Product Characteristics
T <sub>1/2</sub>	Half-life

TGF	Transforming growth factor
TTG	Target treatment group
VEFG	Vascular endothelial growth factor
WHO	World Health Organisation

## **I. RECOMMENDATION**

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Theraloc, an orphan medicinal product in the treatment of children and adolescents with recurrent high-grade glioma in patients where no other therapeutic options are available or appropriate except symptomatic treatment, is not approvable since "major objections" have not been resolved, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

- Quality issues
- Pre-Clinical issues,
- Lack of clinical Pharmacodynamic and pharmacokinetic data,
- Lack of efficacy demonstration.
- Lack of data on immunogenicity
- High rate of SAEs and possible relationship to Theraloc

The applicant has presented only one pivotal, uncontrolled clinical phase II study with 47 patients.

Complete responders were not observed in this clinical trial. Two patients achieved PR and 15 achieved SD and the median time to progression was 50 days and the overall survival was 130 days. The majority of patients failed to continue beyond Week 8.

The value of this study and the interpretability of study results were questioned because of the lack of a comparator. Following the day 120 major concerns and list of questions, the Applicant supplied responses to the major objections and other concerns. The major objection on efficacy and the lack of a comparator in the single pivotal trial was addressed by the Applicant by comparing the Theraloc group with a historical control group. The data provided and comparison between these two groups did not show evidence of benefit in term of overall survival. In addition there was no improvement in severity of symptoms in those treated with Theraloc. In addition the major objections on PK, PD and safety were not resolved along with the majority of other concerns.

## **II. EXECUTIVE SUMMARY**

### **II.1 Problem statement**

This is a new centralised application according to Regulation (EC) No 726/2004 (Article 3(1)), for marketing authorisation for Theraloc (Nimotuzumab 5 mg/ml concentration for solution for infusion) in the indication treatment of children and adolescents with recurrent high-grade glioma.

UK is the Rapporteur and France is the Co-Rapporteur

#### **Original Proposed indication:**

*Theraloc is indicated in the treatment of children and adolescents with recurrent high-grade glioma in patients where no other therapeutic options are available or appropriate except symptomatic treatment.*

**This was altered by the Applicant in the day 120 responses**

#### **New Proposed Indication**

*Theraloc is indicated in the treatment of children or adolescents with resistant or recurrent high-grade glioma*

#### **Posology and method of administration:**

*The recommended dose of Theraloc is 150 mg/m<sup>2</sup> body surface area administered by intravenous infusion over a time period of 30 minutes once a week.*

*Duration of induction treatment is 6 weeks.*

*In patients with non progressive disease treatment should be continued until disease progression by administration of 150 mg/m<sup>2</sup> body surface area once every 2 - 3 weeks.*

### **II.2 About the disease**

Anaplastic astrocytoma (WHO grade III), also known as malignant astrocytoma and high-grade astrocytoma, may arise from a diffuse astrocytoma or may arise de novo without indication of a less malignant precursor. Glioblastoma (WHO grade IV), also known as glioblastoma multiforme, may develop from a diffuse astrocytoma or an anaplastic astrocytoma but more commonly presents de novo without evidence of a less malignant precursor. High-grade gliomas represent approximately 7 to 11% of brain tumours in children (Ruggiero). After an initial surgery, postoperative radiotherapy is generally considered a standard first line treatment in both adult and children. However, despite radical treatment, long-term survival rates remain poor (30% to 40% overall survival for grade 3 and 10% for grade 4 tumours) (Lashford). Although there is evidence that a range of chemotherapeutic agent have modest activity in high-grade gliomas, chemotherapy has failed to make a major impact on outcome (Deangelis).

The primary therapy of GBM includes maximum surgical resection, when feasible, followed by partial brain radiotherapy. Radiotherapy can be combined or followed by chemotherapy. After primary therapy practically all patients will present with recurrent disease.

Although clinical benefit of chemotherapy is only small, cytotoxic agents as BCNU (carmustine) and procarbazine are used for the treatment of GBM. Vinca alkaloids, platinum compounds, methotrexate and cyclophosphamide are also used.

More recently, Temodal (temozolomide) has demonstrated clinical anti-tumour activity in relapsed malignant gliomas, with an acceptable safety profile. In paediatric patients 3 years of age or older, Temodal is indicated for the treatment of recurrent or progressive malignant glioma.

### **II.3 About the product**

Nimotuzumab (Theraloc, h-R3) is a recombinant, humanised monoclonal antibody directed against the human receptor for epidermal growth factor (EGFR), a type I tyrosine kinase receptor of the ErbB family

(ErbB1). In the different studies performed during the pharmaceutical development nimotuzumab is alternatively referred to as hR3, TheraCIMh-R3, CIMAhcr, BIOMAb-EGFR, YMB1000, OSAG 101.

Nimotuzumab is an antineoplastic agent that belongs to the class of EGFR-targeting drugs. By binding to an epitope located in the extra cellular domain of the receptor the antibody blocks the interaction of epidermal growth factor (EGF) and transforming growth factor alpha (TGF $\alpha$ ) with the receptor and inhibits signal transduction.

Nimotuzumab is an IgG subtype 1 kappa monoclonal antibody of approximately 151,000 Daltons that was originally produced by a manufacturing process employing fermentation technology. During the clinical development of the monoclonal antibody, in 2001, changes related to the fermentation process were implemented. All early clinical studies with nimotuzumab (IIC-RD 035, IIC-RD-040, IIC-RD-046, IIC-RD-034, CIMYM-001-CS and YMB1000/004) were initiated before the change of manufacturing process. Currently, nimotuzumab is produced by a continuous culture process. The applicant claims that the bioequivalence of nimotuzumab obtained from these two processes has been shown in *Cereopithecus* monkeys (study RP-003/2002)

#### **II.4 The development programme/Compliance with CHMP Guidance/Scientific Advice**

The rationale for developing the anti-EGFR antibody nimotuzumab in the treatment of EGFR overexpressing tumours has been supported by the pre-clinical findings that nimotuzumab binds selectively ( $K_d$   $10^{-9}$ ) to the EGF receptor and that it has a strong anti-angiogenic, anti-proliferative and apoptotic effect in EGFR overexpressing tumours *in vitro* and *in vivo*.

In adult patients with high-grade gliomas overexpressing EGFR 40 %- 50 % demonstrated amplification often with rearrangement and constitutive activation of the EGFR gene (Liebermann et al 1985, Bredel 1999, Kondo et al. 2004). EGFR overexpression and/or protein expression have been associated with high malignant degree and poor clinical outcome (Mendelsohn and Baselga 2003, Liu et al 2003).

EGFR overexpression has also been observed in children with high-grade glioma.

The dose and regimen for the pivotal study was chosen according to the results that have been obtained in studies with adult patients. Paediatric patients received 150 mg/m<sup>2</sup> which as per applicant corresponded to the optimal dose of 200 mg in adults. The choice of 150mg/m<sup>2</sup> was chosen based on the results of study IIC-RD 053 in adult patients with anaplastic astrocytoma and glioblastoma multiforme, when the 200 mg dose was administered once weekly for 6 weeks.

Clinical trials have been conducted in patients with high-grade glioma, SCCHN, nasopharyngeal cancer, other epithelium derived tumours and pancreatic cancer. Up to September 2007, more than 600 adults and 70 paediatric patients have been exposed to nimotuzumab in completed and ongoing single- and repeated-dose studies.

Scientific advice/Protocol Assistance was given by CHMP for Theraloc 24.6.2005 and 16.1.2006.

## **II.5 General comments on compliance with GMP, GLP, GCP**

### **GLP**

The non-clinical studies were conducted in Cuba except for one study conducted in Canada. Since Cuba is not a member of the OECD, and Canada has no GLP monitoring Authority responsible for pharmaceuticals, the compliance of the studies with the OECD principals of GLP was uncertain. The CHMP requested a GLP inspection of the testing sites, which was conducted in June 2008. On the basis of the inspections, it can be confirmed that the studies cannot be considered to have been performed in compliance with the requirements of the OECD GLP principles as laid down in Directive 2004/10/EC of the European Parliament and Council.

### **GMP**

Although the applicant claims that the drug substance and drug product manufacturing facility *Centre for Molecular Immunology (CIM), Plant No. 2, Calle 216 esquina 15, Atabey, Playa, City of Havana, Cuba* has been recently inspected by the German Inspectorate, it is clear that there are major deficiencies in the control, consistency and validation of the drug substance and drug product manufacturing processes. Considering the deficiencies noted in the manufacturing process and controls, as well as issues noted with out-of-specification (OOS) results, a product-specific inspection request was adopted by CHMP at day 120 to cover the process description and validation from the starting materials to the drug product and to focus on the following points:

- Confirmation that the different claimed “sterile filtrations” at several purification steps are performed in the correct production environment.
- Microbiological monitoring during throughout the process.
- Coherence of the specifications of the in-process controls (IPCs).
- Qualification of reference standards (OOS results, no qualification to the primary reference standard).

The outcome was vital to ascertain whether the consistency and quality of the current drug substance and drug product are assured.

This inspection should have taken place in November 2008 and established whether or not the drug substance and drug product are manufactured according to satisfactory EU-GMP standards.

Importation, packaging, labelling, testing and batch release for EU is undertaken at Oncoscience AG, Hafenstrasse 32,D-22880 Wedel, Germany. This site has been inspected by the German Inspectorate and considered to be acceptable.

### **GCP**

The Applicant appears to be compliant with GCP.

## **II.6 Type of application and other comments on the submitted dossier**

This is a centralised procedure, the application for marketing authorisation for Theraloc (Nimotuzumab 5 mg/ml concentration for solution for infusion) in the indication treatment of children and adolescents with recurrent high-grade glioma.

As per applicant the pivotal study appears to have been conducted in accordance with the principles of GCP, but the overall quality of the report has been compromised by a variety of errors and inconsistencies



in both the conduct and reporting of this study. This is a complete and independent application for a new substance. Relevant Pharmacodynamic/pharmacokinetic/efficacy data were often difficult to find. Most of the provided documents were taken from old type studies. Summaries were of poor quality.

Orphan designation has been granted for Theraloc on 2 September 2004.

### **III. SCIENTIFIC OVERVIEW AND DISCUSSION**

#### **III.1 Quality aspects**

Theraloc consists of a humanized IgG1 kappa antibody (nimotuzumab), recognizing human EGF-receptor. The drug substance, referred to as h-R3 protein (Humanised MAb h-R3 protein) or nimotuzumab, is produced in NSO cell line which has been transfected with pSv2-gpt (IgG heavy chain) and pSv2-hyg (IgG light chain) vectors, at 2 commercial scales. Nimotuzumab is manufactured by and released at the Centre for Molecular Immunology (CIM), Cuba. The drug product (Theraloc) is a 50 mg concentrate for infusion in vial, formulated in sodium chloride, polysorbate 80 and phosphate buffer, to be diluted into 0.9% sodium chloride solution bags. The drug product is produced by CIM, Cuba, and imported, controlled and released in the EU by Oncoscience AG, Hafenstrasse 32,D-22880 Wedel, Germany.

#### **Drug substance**

Nimotuzumab is manufactured using a continuous process. The cell substrate is derived from NSO cell and is stored in a 2-tiered banking system. Master Cell Bank (MCB) and Working Cell Bank (WCB) are controlled according to the same specification, with the exception of the viral testing which is not performed on the WCB. The downstream processing is based on chromatography steps, viral inactivation/reduction steps and several "micro filtrations".

#### **Drug product**

The drug product is presented as a 5 mg/mL concentrate for solution for infusion in a type I glass vial closed with a bromobutyl stopper and an aluminium seal with flip-off cap. Each vial is filled with a nominal volume of 10 mL of solution formulated in phosphate buffer, water for injections, sodium chloride and polysorbate 80.

#### **Stability**

The Applicant claims a 2-year shelf life for the drug product when stored at 2-8°C, and 1 month at 19-23°C. However, taking into account the issues highlighted throughout the dossier (process validation and consistency, comparability, suitability of analytical methods), no shelf life can be given for the drug product.

#### **Conclusions**

From the initial marketing authorisation application and throughout the initial Day 80 assessment it was apparent that this submission, from a quality perspective, was poorly presented with a paucity of relevant data. There were 27 Major Objections (some of which had multiple components) and 73 Other Concerns across the whole of Module 3 identified by CHMP at Day 120. The first of these Major Objections is crucial to the whole Application, namely, the quality of the product used in pivotal clinical trials must be satisfactorily characterised and controlled, and the manufacturing process used to produce these batches must be appropriately validated, using relevant analytical tools, before a marketing authorisation may be envisaged.

From a Quality point of view, it must be re-iterated that the original submission from the applicant was wholly inadequate and major deficiencies were noted in every section of Module 3.

Although the applicant claimed that the drug substance and drug product manufacturing facility *Centre for Molecular Immunology (CIM), Plant No. 2, Calle 216 esquina 15, Atabey, Playa, City of Havana, Cuba* had been recently inspected by the German Inspectorate, it was clear that there are major deficiencies in the control, consistency and validation of the drug substance and drug product manufacturing processes. Considering the deficiencies noted in the manufacturing process and controls, as well as issues noted with out-of-specification results (OOS), a product-specific inspection request was adopted by CHMP at Day 120.

In their response to the Day 120 List of Questions, the Applicant proposed additional controls, validation data, analysis and characterisation studies to remedy all the shortcomings outlined by CHMP. Based on the data provided, the applicant considers their current drug substance and drug product manufacturing processes to be adequately validated, well controlled and capable of producing consistent, fully characterised and stable drug substance and drug product.

However, much of the relevant data was still missing; and the data provided was mainly obtained with batches that do not correspond to the material used in relevant clinical trials.

After assessment of the responses, it is considered that the Applicant's claim cannot be accepted and is not in accordance with the CHMP recommendation given at Day 120 :

- i. All major Quality objections should be resolved before undertaking pivotal clinical studies;
- ii. The results of pivotal clinical studies are considered vital to support any proposed drug substance and drug product specifications.

The interpretation of the issues raised by CHMP at Day 120 is unacceptable and as such, the applicant's attempts to address the major Quality objections and the other concerns are not considered satisfactory.

The major deficiencies observed in Module 3 of the dossier, which included but were not limited to, incomplete or poor process validation, inadequate control of the manufacturing process, unproven comparability between the 2 processes, poor drug substance/drug product characterisation, inadequate validation of analytical procedures and poorly supported stability conclusions meant that the quality of drug product batches used for non-clinical and clinical studies was unacceptable.

The Applicant is also reminded to consider that:

- i) the setting of specifications is a result of an overall development strategy and should be justified and supported through the control of the manufacturing process, drug substance/drug product characterisation studies, stability data, batch consistency, comparability and, as already stated above,
- ii) results of pivotal clinical studies are considered vital to support the specifications.

All 27 major Quality objections and 73 other concerns identified by CHMP at Day 120 are still unresolved and must be addressed once the manufacturing process has been re-developed, such that the Quality and consistency of the product is demonstrated.

Since the Applicant failed to address the pivotal Major Objection, the quality and consistency of the drug product can not be assured, consequently, from a quality point of view, a negative opinion was recommended.

## **III.2 Non clinical aspects**

### **Pharmacology**

The specificity of nimotuzumab to EGFR and its high affinity for human EGFR as well as the suitability of *Cercopithecus aethiops* as species for preclinical testing was determined in binding tests using placental tissue, expressing EGFR at a high density, of various species and confirmed in skin tissue of different

species. A high reactivity of nimotuzumab with various human tumour tissues expressing EGFR was shown, and the affinity of nimotuzumab to tumour tissue was shown to be dependent on EGFR density on the tumour cell surface. The binding of nimotuzumab to tumour cells competed with the binding of natural epidermal growth factor. The mechanism of action of nimotuzumab in vivo was shown to be based not only on the inhibition of tumour cell proliferation by blocking the EGFR but also on antibody mediated cellular cytotoxicity and on complement dependent cytotoxicity. In monolayer and spheroid cultures of tumour cells, nimotuzumab inhibited tumour cell proliferation and reduced the production of VEGF. Nimotuzumab was shown to specifically accumulate in tumour tissue in vivo dependent on the density of EGFR in the respective tumour tissue.

In vivo experiments showed anti-tumour activity of nimotuzumab. The growth of established subcutaneous human A431 growing in SCID mice was markedly reduced by nimotuzumab at a dose level of 1.00 or 0.25 mg/mouse bw every second day even within 8 days. Within 22 days, almost all mice treated with nimotuzumab were tumour free, and remaining tumour tissue in single animals was markedly less vascularised than in controls. In another experiment, nude mice bearing human U87 glioma subcutaneously or intracranially were treated with nimotuzumab at 50 mg/kg bw three times weekly for three weeks with one group receiving radiotherapy in addition. The addition of nimotuzumab to radiotherapy significantly reduced tumour growth in subcutaneous as well as intracranial tumours, while only slight effects of the antibody were observed when given alone. Nimotuzumab reduced the tumour vascularisation. Repeated recurrence of tumours was observed in SCID mice bearing human A431 and treated repeatedly with nimotuzumab until complete tumour regression was achieved. The repeatedly recurring tumours acquired resistance to nimotuzumab. The immunogenic potential of nimotuzumab was demonstrated to be very low. Although nimotuzumab was shown to react with EGFR in different human tissues, mainly of epithelial origin, no corresponding effects on major organ systems were observed in repeated dose toxicity studies in monkeys.

In summary, nimotuzumab was shown to be effective against EGFR bearing tumours in vitro and in vivo alone and in combination with radiotherapy based on specific inhibition of growth and proliferation and based on antibody-mediated immune mechanisms. The studies designated as safety pharmacology evaluated binding to human EGFR in vitro and immunogenic potential in vivo and antibody response in vivo. Functional tests of major organ systems including the CVS, the CNS and PNS and the respiratory system were conducted in the 14-day repeated dose toxicity study. Under the test conditions used, there were no reported adverse treatment related effects.

### **Pharmacokinetics**

The applicant should ensure that all analytical test methods are validated in accordance with the ICH guideline "Validation of Analytical Procedures (Q2A and Q2B)". This issue is considered in detail in the Quality assessment report.

The pharmacokinetics of nimotuzumab were investigated in rabbits following intravenous bolus injection at different dose levels up to about 5.71 mg/kg bw. Nimotuzumab remained in circulation for a long time with mean elimination half-lives between 27.4 and 52.36 hours, increasing dose-dependently, corresponding to the low clearance of 0.38 - 5.5 ml/hour. This slow elimination is a well known characteristic of monoclonal antibodies. The high permanence of nimotuzumab in circulation is also reflected by the mean retention time of 40.2 - 72.46 hours, increasing dose-dependently.

After the intravenous bolus injection of a dose level of 10 mg/kg bw of two different lots produced either by hollow fibre technology or by stirred tank technology to monkeys (*Cercopithecus aethiops sabaeus*), a rapid distribution phase was seen followed by a slow elimination phase. Nimotuzumab remained in circulation for a long time, with elimination half-lives of 6 to 8 days and mean retention times of 7 to 11 days. There was no statistically significant difference between the two lots produced by different

techniques with respect to all measured and calculated parameters. The differences in the technological production process did not appear to affect the pharmacokinetic behaviour of nimotuzumab.

The tissue distribution of nimotuzumab was investigated in baboons using radiolabelled antibody. Highest concentrations were found in liver, kidneys, and urinary bladder. In the liver, the highest concentration was found at 5 minutes after intravenous administration decreasing steadily within the following 48 hours, while in the urinary bladder the concentration increased up to 3 hours after administration and decreased thereafter. All other organs and tissues contained only negligible amounts.

The accumulation of nimotuzumab in established subcutaneous solid tumours in vivo was examined using the human cell line A431 which was inoculated subcutaneously in nude mice. Tumour uptake of nimotuzumab was high with about 5 % of the dose administered at 4 hours and about 4 % at 24 hours. These results were confirmed in nude mice bearing xenografts of the human tumour cell lines U-87, H-125, A431, and MDA-MB-468. The measurement of radioactivity in tumours showed a high accumulation of the radiolabelled nimotuzumab in tumours at 4 hours in all groups, which further increased in H-125, A431, and MDA-MB-468 at 24 hours, while it decreased in U-87.

No investigations on the metabolism and excretion of nimotuzumab were performed, as nimotuzumab is a mammalian protein that is expected to be degraded into amino acids and then introduced into the physiological amino acid metabolism.

### **Toxicology**

Nimotuzumab was tested for acute toxicity upon intravenous bolus injection in Sprague-Dawley rats at dose levels of 1.42, 7.14, 28.57, and 57.14 mg/kg bw. The only drug-related effect observed was a slight increase of body temperature at 28.57 and 57.14 mg/kg, which most probably reflected a reaction to the intravenous injection of a foreign protein from another species. Such a reaction is not expected in humans, as the humanised antibody will not represent a completely foreign protein for patients. No systemic toxic effect was observed.

The repeated dose toxicity of nimotuzumab was tested in rats in two studies with 14 days of intravenous drug administration at dose levels of about 26 and 57.14 mg/kg bw. Besides local effects caused by the mechanical alteration, only minimal changes in haematology and clinical chemistry were seen. No toxic effects were observed, and no target organ of toxicity could be identified. Nimotuzumab was essentially non-toxic up to the highest dose level tested, the NOAEL was above 57.14 mg/kg.

As a second species, *Cercopithecus aethiops sabaeus* was used for repeated dose toxicity studies with 14 days of intravenous drug administration at dose levels of 0.85, 2.85, and 11.4 mg/kg bw. No signs of systemic toxicity were observed, while local effects were caused by the mechanical alteration due to the injection technique. In addition to routine toxicological examinations, functional tests of major organ systems were performed as measurement of heart rate, respiratory rate, electrocardiogram, blood pressure, body temperature, and electrophysiological examinations of the central and peripheral nervous system. No effect of nimotuzumab on any of the examined parameters was observed. Nimotuzumab was essentially non-toxic up to the highest dose level tested, the NOAEL was above 11.4 mg/kg bw.

In a long-term safety pharmacology study, nimotuzumab was administered intravenously to *Cercopithecus aethiops sabaeus* at dose levels of 2.85 or 28.57 mg/kg bw (up to 10 times the equivalent to the human dose) once weekly intravenously for 26 weeks, reflecting the frequency of administration intended to be used therapeutically. No systemic toxic effect was observed in these animals, even at the top dose level.

No plausible rationale has been provided for the use of the dose levels used in the investigation of the toxicity of the product. Therefore there is no reassurance that the studies were conducted with appropriate vigour. The applicant should provide a rationale for the dose levels used.

No studies on possible genotoxic or carcinogenic effects of nimotuzumab were performed. The applicant stated that since antibodies in general are not expected to cause genotoxic effects. Taking into consideration the therapeutic indication the lack of these studies is acceptable.

In addition, no studies on toxicity to reproduction were performed. The applicant claims that all patients, female and male, are at a very advanced stage of disease and in a bad condition and not expected to have the intention or ability to reproduce. This point of view is not accepted. The patients may include females up to 20 years of age, who will have periods of remission. The concern over the design of the toxicity studies means that although there were no reported adverse treatment related effects on male reproductive organs, these studies cannot provide the necessary reassurance. Antibodies are known to cross the placenta. In view of the known physiological role of EGFR and the pharmacological effects of the antibody directed against it, it may be anticipated that this compound will have the potential to cause toxicity to reproduction. Therefore, animal studies are not warranted, since they would only confirm an anticipated effect. Nimotuzumab is contraindicated in pregnancy. Since the effect on male reproduction is not known with certainty, males should use an effective method of contraception during treatment. Section 4.3 of the SPC should be amended accordingly.

The local effects of intravenous bolus injection of nimotuzumab were investigated in rabbits. Only minimal effects caused by the mechanical alterations due to the injection technique were observed. No local effects caused by nimotuzumab occurred.

The non-clinical studies were conducted in Cuba except for one study conducted in Canada. Since Cuba is not a member of the OECD, and Canada has no GLP monitoring Authority responsible for pharmaceuticals, the compliance of the studies with the OECD principals of GLP was uncertain. The CHMP requested a GLP inspection of the testing sites, which was conducted in June 2008. On the basis of the inspections, it can be confirmed that the studies cannot be considered to have been performed in compliance with the requirements of the OECD GLP principles as laid down in Directive 2004/10/EC of the European Parliament and of the Council. This raises a serious question as to the reliability of the data generated in these non-GLP compliant studies.

Major objections were raised in pharmacology about the cross-reactivity of nimotuzumab against receptor domains of other members of the EGF tyrosine kinase receptor family, and in toxicology about the overall design of the studies performed and the impurity profile. In addition, the applicant was requested to clarify other concerns regarding cardiovascular safety pharmacology, the analytical test methods, the pharmacokinetics programme and the potential impact of nimotuzumab on male fertility.

#### **Assessment of responses to non clinical questions**

The applicant's response to the major objection raised in pharmacology is considered satisfactory and the issue can be considered as solved.

#### **Unresolved Issues**

The applicant's discussion is based on results obtained in toxicity studies which were conducted in *Cercopithecus aethiops* monkeys. However, these studies were not performed in compliance with the requirements of the OECD GLP principles as laid down in Directive 2004/10/EC of the European Parliament and Council. This raises a serious question as to the validity and reliability of the data generated by the non-GLP compliant studies. Therefore, the arguments presented by the applicant to answer these questions cannot be taken into consideration.

It is noted that further to the first evaluation of the dossier by the CHMP, the applicant initiated a 26-week study in *Cynomolgus* monkeys which is currently ongoing. It seems important to wait for the final results of this study as it may allow the applicant to answer questions 102, 104 and 107. As this study is being

conducted at ITR Laboratories in Canada and that this country has no GLP monitoring Authority responsible for pharmaceuticals, its GLP status will have to be assessed by GLP inspectors.

The levels of impurities tested in the toxicity studies do not support the proposed acceptance criteria. Furthermore the applicant’s discussion of the question of impurities also relies on data from toxicity studies that were not GLP-compliant and, therefore, cannot be taken into consideration.

Taking into account the lack of GLP compliance of studies initially submitted, the use of unvalidated analytical test methods, and the lack of relevant studies, it is considered that the pharmacokinetics of nimotuzumab is not completely described in animals. The applicant now provides results of a TK study obtained after single administration of nimotuzumab to Cynomolgus monkeys. However, tissue distribution of nimotuzumab still remains unknown. To complete the currently limited nonclinical PK package, the applicant should at least perform cross-reactivity studies on a range of human tissues as requested by guideline ICH S6 (the list of tissues to be tested is detailed in the “Points to consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use” [FDA/CBER, 1997]).

### III.3 Clinical aspects

#### Pharmacokinetics

The Applicant has provided pharmacokinetic results mainly taken from the following studies:

**Table I:** *Main pharmacokinetic studies*

Study	Indication	Design	Number of patients included/ treated	Treatment
<b>CIMYM-001-CS</b>	Epithelial tumours	Phase I, single dose	12	99mTc-nimotuzumab
<b>IIC RD-034</b>	Epithelial tumours	Phase I single dose	25	99mTc-nimotuzumab
<b>IIC RD-035</b>	Epithelial tumours	Phase I, single-dose	12	99mTc-nimotuzumab
<b>IIC RD-EC040</b>	SCCHN	Phase Ib/IIa	14	Nimotuzumab + RT
<b>IIC RD-EC046</b>	SCCHN	Phase Ib/IIa, un-controlled, open-label	10	Nimotuzumab + RT

Pharmacokinetic data after single dose administration of 50, 100, 200 and 400 mg suggested a non-linear pharmacokinetic behaviour of nimotuzumab between the 50 and 200 mg dosages. The area under the curve (AUC) and elimination half-life increased with dose, while increasing concentrations of the antibody lead to a decrease in plasma clearance between the doses of 50 and 200 mg. The peak serum concentrations of nimotuzumab after infusion were dose dependent.

The increase in the elimination rate, volume of distribution, and half-life time was observed to be higher than expected for a dose proportional manner. The increasing doses of nimotuzumab led to decreasing values of plasma clearance of nimotuzumab. C<sub>max</sub> increased dose-dependently (IIC RD-035).

The optimal biologic dosage was defined as the lowest dose at which complete saturation is reached in the systemic clearance of the monoclonal antibody. This is based on the hypothesis that the zero-order elimination is associated with the saturation of the EGF receptors of the peripheral compartment. According to the data, it was concluded that the 200 mg dose represented a biologically active dose.

Pharmacokinetics of multiple doses of 200 and 400 mg were evaluated in patients with SCCHN (IIC-RD-046). At the 200 mg dose, the half life ( $t_{1/2}$ ) was between 2.5 and 3.7 days for an average value of  $3.1 \pm 0.8$  days. At the 400 mg dose, values ranged between 1.4 and 4.2 days, with an average value of  $2.6 \pm 1.0$  day. In study BN-001 PED-04 mean AUC value determined in children was 20.4 mg/ml x h. Cmax was 127 µg/ml, T1/2  $\alpha$  was 119 h and the Vss was 1.65 l. Total clearance was determined to be 12 ml/h. These results demonstrated that AUC and the terminal T1/2 increased with dose, while increasing serum concentrations of nimotuzumab led to a decrease in the clearance between doses. The differences in AUC as well as Vss, Cmax, and clearance with increasing applications of nimotuzumab were significant confirming the pharmacokinetic results obtained in adults.

The applicant has given minimal data, and it is not always clear if the data is not available, or just not studied: data of the mean volume distribution at steady state, dose proportionality, data of peak and trough concentrations of nimotuzumab, data of intra- and inter-individual variability.

Taken together, the provided results do not allow drawing any formal conclusions on the pharmacokinetics of Nimotuzumab

### **Pharmacodynamics**

The growth of a majority of malignant gliomas is stimulated by growth factors such as EGF (epidermal growth factor). Growth factors are present in the blood like other proteins and bind to a specific site on the tumour cells. This site is called a receptor for the growth factor. If an antibody against this receptor is present in the human blood it will bind to the receptor and block the site to binding of the growth factor.

Thus the growth factor can no longer stimulate the growth of the malignant cells.

The applicant has discussed mechanism of action shortly, but the applicant has not described the EGFR status of children with HGG. The relationship between plasma concentration and efficacy is not clear.

In conclusion, the quality of the data submitted by the Applicant was extremely poor and does not allow assessment of the pharmacodynamic parameters of Nimotuzumab.

### **Clinical efficacy**

No controlled clinical studies to the claimed indication have been performed with Theraloc. The pivotal evidence of efficacy in this submission is presented by one uncontrolled, single arm, phase II study BN-001 PED-04 with 47 patients.

#### *Dose-response studies and main clinical studies*

As no pharmacokinetic information was available for children and adolescents at the time study BN-001 PED-04 was initiated, the dose and regimen for this pivotal study was chosen according to the results that have been obtained in studies with adult patients.

It is not clear why there was no reference arm, as best supportive care or temozolamide, which is approved for glioma.

There is discrepancy between studied patients and the proposed indication. Included patients had lack of a curative standard therapy or lack of a curative-intended therapy currently being evaluated in a countrywide GPOH therapy-optimizing study, but the claimed indication was where no other therapeutic options are available or appropriate except symptomatic treatment. The indication should present the studied patients.

Although nimotuzumab is directed against the human receptor for epidermal growth factor (EGFR), the applicant has not presented the EGFR status of studied patients.

The applicant has presented not clearly the previous therapy, and as per the applicant 20/47 patients received chemotherapy (11 patients received temozolomide) after the pivotal study, there is a possibility that all the patients were not maximally treated, although the proposed indication is for patients *where no other therapeutic options are available or appropriate except symptomatic treatment*.

In the synopsis of pivotal study the primary efficacy endpoint was the objective response rate (proportion of patients in whom CR, PR, or SD was documented) with response documented according to RECIST. Secondary efficacy endpoints were the progression-free survival time, the survival time, the duration of response, and the severity of two cardinal symptoms per patient.

But in study report: The primary efficacy endpoint was the overall best response rate and the secondary objectives of this study were to determine the progression-free survival, the influence of the drug on disease cardinal symptoms and on toxicity.

In the study protocol primary endpoint is assessment of response rate and secondary objectives are assessment of progression free interval (PFI), toxicity and symptom control.

A number of inconsistencies exist between the statistical methods described in the amended protocol, those included in the study report and the actual presentation of the results of the analysis in the report.

There were 13 patients (28.9 %), aged on average 12.15 years, with a glioblastoma (WHO IV) at baseline, 11 patients (24.4 %), aged on average 10.73 years, with an anaplastic astrocytoma (WHO III), and 21 patients (46.6 %), aged on average 8.81 years, with an intrinsic glioma of the pons. On average, the patients were enrolled 1.04 years after the first diagnosis into the study.

On average (median), the patients terminated the clinical trial after 8 weeks.

As there were only 12 patients in the PP population, who were observed longer than 8 weeks, the number of patients is limited to make confident conclusions.

The primary efficacy variable was the objective response rate. Patients were called responders if they had complete remission (CR), partial remission (PR), or stable disease (SD). The overall response was evaluated during week 8 and during week 21. This interval between is unusual long, especially for this group of patients.

### **Best overall response in different high-grade glioma subgroups**



		Glio- blastoma  (n=13)	Anaplastic astrocytoma  (n=11)	Intrinsic glioma of the pons  (n=21)	All patients  (n=45)
Best overall response	n (%)	3 (23.1 %)	3 (27.3 %)	11 (52.4 %)	17 (37.8 %)
	95%CI	6.6 %; 52.0 %	7.9 %; 61.0 %	29.8 %; 72.4 %	23.8 %; 53.5 %
CR	n (%)	-	-	-	-
PR	n (%)	0	1 (9.1 %)	3 (14.2 %)	4 (8.9 %)
SD	n (%)	3 (23.1 %)	2 (18.2 %)	8 (38.1 %)	13 (28.9 %)
PD	n (%)	10 (76.9 %)	8 (72.7 %)	10 (47.6 %)	28 (62.2 %)

All the results are presented in PP population, not in ITT. There were no reports of complete response and only four of the patients experienced a partial response with the remainder reporting stable disease. Most responders were observed in the subgroup of patients with a diffuse intrinsic pontine glioma. The confidence intervals were wide due to the small numbers of patients. Two patients were documented as SD in the CRFs, but they showed a PD. One patient had only one day between start and end of response, in the study report it was called SD.

The median time to progression was 50 days (95 % CI: 44 to 54 days).

The majority of the patients reported stable disease and only 2 of the 17 responders demonstrated a partial response. There were no patients with a complete response to therapy. As there is no comparator in the pivotal study, any interpretation of these results is extremely difficult unless response to standard care, or no treatment, is known precisely.

The median survival time was 130 days (95 % CI: 99 to 161 days).

Any comparison of duration of response by diagnosis will be of limited value due to the small number of patients (17) included in the analysis, especially with the majority of patients (11) in one subgroup and only 3 patients in each of the other two.

The patient's mean severity of cardinal symptoms seems to increase during the time in glioblastoma and anaplastic astrocytoma groups.

#### *Supportive study(ies)*

RD-EC053 was a multi-centre, open-label, Phase I/II clinical trial conducted in patients (n=29) with glioblastoma (WHO grade IV, n = 16) and anaplastic astrocytoma (WHO grade III, n = 13) who had previously undergone biopsy or surgery for their condition in order to assess the safety and efficacy of nimotuzumab as an adjunctive treatment to radiotherapy.

A total of 5 patients had a complete response to treatment with nimotuzumab plus radiotherapy, while 6 patients had a partial response to treatment. Three patients had progressive disease and others had stable disease. The mean and median survival was 24.09 and 22.17 months, respectively, for all patients in the ITT population. For AA patients, mean overall survival time was 36.03 months. For GBM patients, median overall survival time was 16.30 months.

#### **Clinical safety**

### *Patient exposure*

The mean number of infusions, that patients received was 6.53, it means 6 weeks treatment.

### *Adverse events*

A total of 43 patients (91.5 %) experienced a sum of 157 non-serious adverse events (AEs) in the course of this clinical trial. The most frequent adverse events were according to System Organ Classes (SOCs) of MedDRA “General disorders and administration site conditions” (n=39, 83.0 %), “Nervous system disorders” (n=24, 51.1 %), “Gastrointestinal disorders” (n=17, 36.2 %), “Skin and subcutaneous tissue disorders” (n=14, 29.8 %), “Infections and infestations” (n=11, 23.4 %), and “Blood and lymphatic system disorders” (n=9, 19.1 %).

Nervous system disorders are common in this patient population. There were also three cardiac disorders: arrhythmia, extrasystole and cardiac arrest. It is not clearly described how many AEs were related to study drug.

### *Serious adverse events and deaths*

A total of 49 SAEs were documented for 37 patients (78.7 %). Thirty patients (63.8 %) died during the course of the clinical trial (without follow-up information after study end). In all cases, the investigators assessed the causal relationships of death and study drug application as “unrelated” or “improbable”. The most common SAEs by SOC were: “Nervous System Disorders” (n=30), “General disorders and administration site conditions” (n=23), and “Respiratory, thoracic and mediastinal disorders” (n=11). No serious side effects related to the study medication were observed.

The applicant presents the early death table, in which majority of deaths were not tumour related, but the reason for death is not explained.

### *Laboratory findings*

No relevant change was observed in any quantitative laboratory variable.

### *Immunological events*

Like other monoclonal antibodies nimotuzumab has the potential to induce an immune response and to form antibodies when administered to patients.

The immunogenicity of nimotuzumab was evaluated in 6 clinical trials, where human anti human antibodies (HAHA) and human anti mouse antibodies (HAMA) were measured to determine the anti-idiotypic response against nimotuzumab. From the data there were a total of 3 patients with antibody development. In the SmPC section 5.1 the applicant mentioned only one case.

### *Discontinuation due to AES*

## **AEs, which led to interruption of treatment**

### **Pharmacovigilance system**

The CHMP considers that the Pharmacovigilance system as described by the Applicant generally fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Provided that the Applicant addresses the following issue:

- Submits a copy of the organisation chart in English;

The flow diagram indicating the flow of safety reports does not cover how reports are submitted to the Competent Authorities if paper reporting is in operation

### **Risk Management Plan**

The extent of the safety database in the proposed indication should be carefully presented, together with a summary of the missing information. This is particularly relevant as there are only 47 patients in the child/adolescent age-group. The limitations of the small safety database should be described more fully.

The adverse events observed in the clinical studies should be summarized and presented as described in the template.

More information should be given on the adverse events experienced by patients using product from the batch which caused a large number of serious adverse events. There should also be more information. The risk of anaphylactic reaction should be considered an identified risk as it is a known class effect, and has also been observed once in clinical studies. More information on this case should be presented.

Hepatobiliary disorders are very common reactions in patients treated with other EGFR targeted products and should be included in section 1.8.

### **Assessment of responses to clinical questions**

The major objection of insufficient evidence of adequate dose-finding and pharmacokinetic studies in children remains. No population pharmacokinetics was performed. The need for adequate PK and PD readouts to choose an appropriate dose range in children is central. This has not been done.

The efficacy major objection was addressed by a secondary analysis comparing with a historical control group. From the raw data provided it was clear that all patients in the Theraloc group died compared with 92.2% of the historical control group. In addition the duration of diagnosis to last observation ranged from 178-467 days for the Theraloc group compared with 396.7 to 2695 in the historical control group. This data shows that the Theraloc group all died in a shorter period of time than the historical control group. In addition the Updated Clinical Study report stated that “The patient’s mean severity of cardinal symptoms did not change relevantly during the course of the clinical trial.” The data does not support efficacy on survival, length of survival and severity of symptoms in the Theraloc group. In addition 55% of the paediatric brain tumours examined were negative for EGFR which is less than expected for this group. This is less than expected as 80% of high grade non-brainstem paediatric gliomas have been demonstrated to express EGFR (Bredel et al. Clin Cancer Res, 1999: 5: pp1786-1792). In addition Pollack et al 2006, showed that EGFR expression was increased in 6/9 Anaplastic Astrocytomas and 6/13 GBMs. The lack of any strong correlation between EGFR expression as detected and clinical outcome is difficult to interpret due to the lack of clinical efficacy.

The major objection on lack of adequate information on immunogenicity in children was not resolved as the response stated that no antibody results were available from study BN-001 PED-04.

The major objection on lack of adequate safety data has not been resolved as without a parallel control group it is difficult to assess the likely relatedness of the test medication to the numerous SAEs seen in different patient groups and to ascertain the safety profile of Theraloc in paediatric malignant GBM, AA and intrinsic pons gliomas.

The Applicant’s responses did not lead to resolution of any of the major objections nor to the majority of the other concerns related to clinical aspects. There was no assessment of inter- or intra-individual PK data in children; inadequate PD data; lack of justification for dose selection in the proposed indicated group; unclear documentation relating to steroid dosage prior to radiological assessment; evaluations of clinical state relied in many cases limited to clinical assessment; failure to comply with RECIST

guidelines in order to classify patients' status with repeat MRI assessments, no assessment of immunogenicity in children; increased adverse events with a particular batch of Theraloc; lack of post-marketing safety events (in countries where Theraloc is marketed), and a lack of evidence of efficacy either in terms of overall survival, length of survival or severity of symptoms

#### **IV. ORPHAN MEDICINAL PRODUCTS**

Orphan designation has been granted for Theraloc in 2.9.2004.

#### **V. BENEFIT RISK ASSESSMENT**

##### **V.1 Clinical context**

This application for Theraloc, an orphan medicinal product, is for the treatment of children and adolescents with recurrent high-grade glioma in patients where no other therapeutic options are available or appropriate except symptomatic treatment.

##### **V.2 Benefits**

No controlled clinical studies to the claimed indication have been performed with Theraloc. The pivotal evidence of efficacy in this submission is presented by one uncontrolled, single arm, phase II study BN-001 PED-04 with 47 patients.

The indication does not reflect the studied population. Patients who were included in the study had a lack of a curative standard therapy or lack of a curative-intended therapy currently being evaluated in a countrywide GPOH therapy-optimizing study but the claimed indication is: where no other therapeutic options are available or appropriate except symptomatic treatment.

Response rate in oncology is usually defined as the percentage of patients whose cancer shrinks or disappears after treatment. The applicant has included patients with stable disease as responders. The applicant has not described the minimum duration of response needed to qualify as a responder.

Complete responders were not observed in this clinical trial. Responders (i.e., SD+PR) were 3 patients in glioblastoma group, 3 patients in anaplastic astrocytoma and 11 in intrinsic glioma group.

Company has not proved that nimotuzumab is more efficacious or safer than other treatments.

The value of this study and the interpretability of study results are questioned because of the lack of a comparator. The studied patients were heterogeneous. The different diagnosis groups have different prognosis. The Applicant was asked to address major objections relating to PK efficacy and safety as well as 87 other concerns.

The Applicant's responses to the major objections included a secondary analysis of the Theraloc group compared with a historical control group. The Applicant's responses did not lead to resolution of any of the major objections of PK safety and efficacy nor to the majority of the other concerns related to clinical aspects

In conclusion, there are no clear benefits demonstrated with this product for the indication sought. Efficacy has thus not been shown.

### **V.3 Risks**

- Demonstrated risks

Lack of efficacy. When compared with the historical control group in terms of overall survival or length of survival. In addition those receiving Theraloc did not have a reduction in the severity of their symptoms. The lack of efficacy remains a major concern.

Variability of incidence of adverse events with different batches of Theraloc. This may be related to shipping and storage as suggested by the Applicant, but may also be related to the quality of the product batches.

A proper assessment of the safety profile was hampered by the small number of patients and the fact that pivotal study was an uncontrolled study. This was not resolved with the secondary analysis and responses provided by the Applicant in the day 120 responses. There are a number of serious adverse events affecting various organ systems. The likely relationship of the SAEs to the test product has not been explained. The lack of safety data especially concerning cardiac function, hepatic function and deaths, is considered a major concern.

- Potential risks

The quality of product uncertain. The quality and consistency of the drug product can not be assured. The major deficiencies observed in Module 3 of the dossier, which included but were not limited to, incomplete or poor process validation, inadequate control of the manufacturing process, unproven comparability between hollow fibre and stirred tank fermentation processes, poor drug substance/drug product characterisation, inadequate validation of analytical procedures and poorly supported stability conclusions meant that the quality of drug product batches used for non-clinical and clinical studies was unacceptable.

The Applicant has not addressed immunogenicity in the proposed group.

### **V.4 Balance**

The quality and consistency of the drug product can not be assured. The clinical efficacy of Theraloc has not been established in the claimed indication. In the absence of established efficacy, the demonstrated and potential risks are not considered acceptable. The benefit-risk balance for Theraloc in the claimed indication is negative.

### **V.5 Conclusions**

The overall B/R of Theraloc is negative.