TheraCIM™

Nimotuzumab

Injection Solution

Composition

TheraCIM™ (Nimotuzumab) is formulated as a colorless sterile solution in 10 mL of water for injection

Each vial (10 mL) contains:

Nimotuzumab	50.0 mg
Dibasic sodium phosphate (Na_2HPO_4)	18.0 mg
Monobasic sodium phosphate (NaH_2PO_4)	4.5 mg
Sodium chloride	86.0 mg
Polysorbate 80	2.0 mg
Water for injection	ad 10 mL

Description:

TheraCIM™ (Nimotuzumab) is a recombinant humanized monoclonal antibody that binds to the extracellular domain of human epidermal growth factor receptor. The humanized antibody (IgG1) was obtained by cloning the CDRs of the murine IgG2a monoclonal antibody (ior egf/r3). A reshaped antibody was constructed using the light and heavy chains of REI and Eu, respectively, as human immunoglobulin framework for CDR-grafting. **TheraCIM™** is produced through mammalian cell culture of non-secreting NSO cells and has a molecular weight of 151 KD.

Clinical Pharmacology

Nimotuzumab binds with intermediate affinity and high specificity to the extracellular domain of epidermal growth factor receptor (EGFR, HER1, c-Erb-1). Nimotuzumab blocks the binding of the EGF to its receptor and inhibits *in vivo* and *in vitro* tumor cell growth. Nimotuzumab has a potent anti-angiogenic, anti-proliferative and pro-apoptotic effects in those tumors that overexpress the EGFR.

Pharmacokinetics

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

Nimotuzumab clearance (CL) decreased from 1.08 to 0.34 mL/h/kg as the dose increased from 50 to 200 mg, and at doses >200 mg, it appeared to plateau. Pharmacokinetic analysis of plasma clearance curves showed terminal half-life times ($t_{1/2\beta}$) for 50, 100, 200, and 400 mg doses of 62, 82, 302, and 304 hours, respectively. Under normal

physiological conditions, the percentage of injected dosage discharged through urinary tract are 21.1% for 50 mg, 28.20% for 100 mg, 27.36% for 200 mg, 33.57% for 400 mg.

Indications

- Chemotherapy resistant high-grade gliomas in children / adolescent with histologically proven diagnosis of WHO grade III or IV, radiologically proven progressive disease (PD) following primary or relapse treatment.
- Treatment of locally advanced non-nasopharyngeal Squamous Cell Carcinoma of Head and Neck (SCCHN) (Stage III or IVA/B) in combination with concurrent chemoradiotherapy.

Dosage

Glioma in children & adolescents

Dosage for glioma in children & adolescents: Monotherapy in two consecutive phases, induction phase and consolidation phase. During induction phase, Nimotuzumab is given at 150 mg/m^2 BSA weekly for 6 weeks. After induction phase, patient without progressive disease upon 8th week evaluation will be treated in the consolidation phase, where Nimotuzumab is given at 150 mg/m^2 BSA every three weeks until disease progression.

Patients	Dosage		Concurrent Therapy
Children / adolescent	***Induction phase***	150 mg/m^2 BSA every week for 6 weeks	NA
	Consolidation phase	150 mg/m^2 BSA every 3 weeks until disease progression	NA

Locally Advanced Non-Nasopharyngeal Squamous Cell Carcinoma of Head and Neck (SCCHN)

Nimotuzumab 200 mg fixed dose once a week for 7 weeks and cisplatin + radiotherapy regimen. Dosage for chemotherapy: Cisplatin 30 mg/m^2 administered as IV infusion weekly for 7 weeks. Dosage for radiotherapy: 2 Gy daily for 5 days a week, total 66-70 Gy over a period of 6.5-7 weeks.

Efficacy and safety of Nimotuzumab in pediatric patient with SCCHN have not been established.

Administration

Glioma in children & adolescents

The recommended dosage of **TheraCIM^{TM}** (Nimotuzumab) is administered as continuous intravenous (IV) infusions as monotherapy for relapsed glioma in pediatric/adolescent. Nimotuzumab is diluted in 250 mL of 0.9% sodium chloride solution and administered intravenously within 30 minutes for pediatric/adolescent patients. Pretreatment with Diphenhydramine is recommended to minimize possibility of infusion reaction.

Locally Advanced Non-Nasopharyngeal Squamous Cell Carcinoma of Head and Neck (SCCHN)

TheraCIM™ will be administered as a continuous intravenous infusion in 250 mL of 0.9% sodium chloride solution over 60 minutes once a week, for 7 weeks.

Contraindications

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

Warnings and Precautions

1. **TheraCIM™** (Nimotuzumab) should be administered with cautions in patients who have previously received treatment with the murine monoclonal antibody ior egf/r3. **TheraCIM™** (Nimotuzumab) should be used with caution in patients with chronic diseases in decompensate phase, such as cardiac dysfunction, diabetes mellitus or arterial hypertension or in patients with history of severe allergic reaction.
2. The product should be applied under the supervision of skilled clinical doctors.

Use in Pregnancy and Lactation

Use in Pregnancy

Effects of Nimotuzumab on pregnancy have not been studied. However, animal studies have shown that at the embryonic stage, lack of EGFR can cause lack of maturation of the epithelium and postnatal death. EGFR has been implicated in the control of prenatal development and hence may be essential for normal organogenesis, proliferation and differentiation in the developing embryo. Human IgG1 is known to cross the placental barrier; therefore the antibody has the potential to be transmitted from the mother to the developing fetus. The use of Nimotuzumab during pregnancy is not recommended. The antibody should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit outweighs the potential risks to the fetus. If the patient becomes pregnant while receiving this drug, she should be informed of the potential hazard to the fetus and/or the potential risk of loss of the pregnancy.

Use in Lactation

Nimotuzumab is secreted in human milk, therefore it is not recommended to use in lactating women. No recommendation is made on the potential benefit versus risk of administering Nimotuzumab to nursing mothers.

Pediatric Use

A phase II clinical study in pediatric patients with brain tumors is done and showed no significant adverse events related to Nimotuzumab. Efficacy in heavily pretreated relapsed high grade gliomas in children and adolescents has been demonstrated in the phase II study. The repeated application of Nimotuzumab as monotherapy was well tolerated and safe. The clinical deteriorations were mostly associated with complications of the tumor disease, tumor progressions or, rarely, with another concomitant disease.

In particular no allergic reactions or severe skin or gastrointestinal toxicity were observed. No safety concerns arose from laboratory tests, vital signs, or physical

examination findings. No severe hematological or non-hematological side effects associated with the Nimotuzumab monoclonal antibody were seen. A phase III study of newly diagnosed diffuse intrinsic pontine glioma in pediatric/adolescent is currently ongoing. The most frequently reported AE related to study treatment includes erythema, leucopenia, nausea, vomiting, fatigue and headache.

Efficacy and safety of Nimotuzumab in pediatric patient with SCCHN have not been established.

Adverse Reactions

Common adverse events with recommended dose reported following administration of Nimotuzumab that are at least possibly related to Nimotuzumab include chills, fatigue, headache, nausea, pyrexia, tremors, vomiting, anemia, arterial hypotension or hypertension, fever and increase of the alkaline phosphatase, ALT and AST.

In the pediatric trial, non-serious adverse events considered at least possibly related to Nimotuzumab included erythema, leucopenia, fatigue, headache, nausea and vomiting. Rare adverse events reported were myalgia, somnolence, disorientation, hematuria, and elevated liver functions enzymes.

In clinical experience, potentially fatal allergic reaction was very rarely reported. This event includes rapid and severe hypotension and urticaria.

In the phase III trial of patients with SCCHN, adverse events considered at least possibly related to Nimotuzumab in combination with chemoradiotherapy included mucositis and maculopapular rash. Mucositis and maculopapular rash were reported more frequently in the nimotuzumab plus chemoradiotherapy combination group than in the chemoradiotherapy alone group. The other adverse events occurred with similar frequency in the chemoradiotherapy group and Nimotuzumab in combination with chemoradiotherapy included hematologic adverse events (anemia, neutropenia, febrile neutropenia, thrombocytopenia), biochemical adverse events (increased serum creatinine, AST, ALT), electrolyte disturbance (hyponatremia, hypokalemia, hypomagnesemia), local radiation adverse events (radiation dermatitis, odynophagia, dysphagia), gastrointestinal adverse events (nausea, vomiting, weight loss), other adverse events (stroke, tinnitus). Long-term adverse events (> 90 days) included xerostomia, dysgeusia, subcutaneous fibrosis, decreased shoulder range of motion, dysphagia, impaired hearing caused by sensorineural hearing loss, were also similar between 2 arms.

Drug Interactions

The interaction of Nimotuzumab with other cytostatic drugs has not been evaluated to date, although there does not appear to be any significant interaction with co-administered gemcitabine.

Synergistic effects and potentiation of the anti-tumor activity had been already shown when other EGFR inhibitors have been used in combination with chemotherapy.

Effects on Ability to Drive and to Use Machine

Effect of Nimotuzumab on the ability to drive or use machine is not known. Caution should be exercised for patients who will drive or use machine after Nimotuzumab administration.

Overdosage
A phase I study conducted in Canada has demonstrated that doses up to 800 mg/week are safe and well tolerated in humans.

Preparation for Administration
1. Do not shake the content of the vial. A vigorous shaking could denature the protein and affect the biological activity of the product.
2. Product should be inspected visually for particulates and discoloration prior to administration, if these are present do not use the product.
3. Use a sterile syringe and appropriate aseptic technique. Remove the cap from the vial containing **TheraCIM™** (Nimotuzumab) and clean the top of the vial with anti-bacterial solution, and insert the needle into the vial to extract the content.
4. The **TheraCIM™** (Nimotuzumab) at the selected dosage should be diluted in 250 mL of 0.9% sodium chloride.
5. **TheraCIM™** (Nimotuzumab) does not contain any preserving agent in its formulation; therefore it should be used immediately after opening the vial for preparing the infusion.

Storage Conditions
1. **TheraCIM™** (Nimotuzumab) should be stored in refrigerator at 2-8°C. The biological activity of the antibody may be lost after freezing and thawing. Do not freeze or shake.
2. **TheraCIM™** (Nimotuzumab) diluted into 0.9% sodium chloride is physically and chemically stable for 72 hours, at a temperature not exceeding 27°C. If these limits are exceeded, the infusion must be rejected.

Presentation
1 box contains 2 vials of **TheraCIM™** Solution for Injection. Each 10 mL vial contains 50 mg of Nimotuzumab

Reg. No.: DKI1326500143A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
Center of Molecular Immunology,
Havana, Cuba.

Imported and marketed by:
PT KALBE FARMA Tbk.
Bekasi - Indonesia

***PACKAGE LEAFLET*: INFORMASI UNTUK PASIEN**
THERACIM
Nimotuzumab 50 mg/10 mL

Bacalah seluruh *leaflet* ini dengan hati-hati sebelum Anda mulai menggunakan obat ini untuk mendapatkan informasi yang penting untuk Anda.

- *Leaflet* ini berisi pertanyaan-pertanyaan yang umum ditanyakan mengenai Theracim.
- *Leaflet* ini tidak mengandung semua informasi yang tersedia.
- Semua obat mengandung risiko dan manfaat. Dokter Anda telah mempertimbangkan risiko yang dialami dengan pemberian Theracim dengan manfaat yang diharapkan untuk Anda.
- Jika Anda memiliki pertanyaan selain yang terdapat dalam *leaflet* ini, tanyakan pada dokter atau apoteker.
- Jika Anda mengalami efek samping, konsultasikan dengan dokter, apoteker, atau perawat. Efek samping ini mencakup efek samping apapun, termasuk yang tidak terdapat dalam *leaflet* ini.

1. Apa itu Theracim dan apa komposisi Theracim?

Theracim mengandung bahan aktif *nimotuzumab*, yang termasuk dalam golongan antibodi monoklonal. Theracim dapat digunakan untuk pengobatan kanker tertentu.
Theracim secara selektif mengikat protein yang disebut dengan *epidermal growth factor receptor* (EGFR)/*human epidermal growth factor receptor 1* (HER1) pada jenis kanker tertentu. EGFR ditemukan dalam jumlah besar pada permukaan beberapa sel kanker. Jika Theracim mengikat EGFR, akan memblok pengikatan *epidermal growth factor* (EGF) dengan reseptornya sehingga diharapkan dapat mencegah pertumbuhan dan penyebaran sel-sel kanker.

2. Apa bentuk sediaan Theracim?

Theracim tersedia dalam bentuk cairan injeksi dalam kemasan vial yang mengandung *nimotuzumab* 50 mg/10 mL.

3. Bagaimana pemerian atau deskripsi Theracim?

Theracim diformulasikan sebagai larutan steril tidak berwarna.

4. Apa kegunaan dari Theracim?

Theracim digunakan untuk mengobati glioma (jenis tumor yang dijumpai pada otak dan sumsum tulang) derajat III atau IV pada anak dan remaja.
Theracim dapat juga digunakan untuk pengobatan kanker kepala leher non-nasofaring derajat III atau IVA/B pada dewasa.
Untuk terapi glioma, Theracim diberikan secara tunggal.
Untuk terapi kanker kepala leher, Theracim diberikan bersama kemoterapi dan radioterapi.

5. Bagaimana cara pemberian Theracim?

Theracim harus disiapkan oleh tenaga kesehatan profesional (apoteker) sebelum diberikan dan akan diberikan di rumah sakit oleh dokter atau perawat.
Theracim diberikan secara infus intravena selama 30-60 menit.

6. Berapa dosis pemberian Theracim?

Glioma: Selama fase induksi, Theracim diberikan dengan dosis 150 mg/m^2 luas permukaan tubuh setiap minggu selama 6 minggu. Setelah fase induksi, pasien tanpa progresivitas penyakit setelah evaluasi pada minggu ke-delapan, akan diobati pada fase konsolidasi di mana Theracim diberikan dengan dosis 150 mg/m^2 luas permukaan tubuh setiap 3 minggu dan terapi dihentikan jika terjadi progresi penyakit.
Kanker kepala leher: Theracim 200 mg dosis tetap diberikan setiap minggu selama 7 minggu dalam kombinasi dengan *cisplatin* dan radioterapi.

7. Apa yang dilakukan jika terapi Theracim terlewatkan?

Jika dosis Theracim terlewatkan, dokter akan menjadwalkan kembali jadwal terapi berikutnya.

8. Pada keadaan apa Theracim tidak boleh diberikan?

Theracim tidak boleh diberikan pada pasien dengan riwayat hipersensitivitas terhadap *nimotuzumab* atau komponen apapun dari produk ini.

9. Apa yang perlu diperhatikan jika Anda akan menggunakan Theracim?

Sebelum mendapatkan terapi Theracim, beritahukan dokter Anda jika:

- Anda memiliki riwayat:
  - Gangguan fungsi jantung
  - Diabetes melitus (kencing manis)
  - Hipertensi arteri (peningkatan tekanan darah arteri)
  - Reaksi alergi berat
- Anda hamil atau berencana untuk hamil
- Anda alergi terhadap obat lain atau zat lainnya seperti makanan, pengawet, atau pewarna.

Beritahukan dokter atau perawat segera jika Anda memiliki tanda atau gejala berikut:

- Tanda dan gejala reaksi alergi atau anafilaktik atau reaksi infus:
  - Pembengkakan wajah, bibir, lidah, atau tenggorok dengan kesulitan bernapas.
  - Pembengkakan bagian tubuh yang lain.
  - Sesak napas, mengi **(**suara bernada tinggi yang terdengar saat sedang bernapas**),** atau gangguan bernapas.
  - Ruam (kemerahan), gatal pada kulit.
  - Mual
  - Demam, menggigil.
  - Merasa lelah.
  - Sakit kepala.

Jangan hentikan terapi Theracim tanpa berdiskusi dengan dokter.

10. Obat apa yang harus dihindari jika menggunakan Theracim?

Interaksi *nimotuzumab* dengan obat sitostatik lainnya sampai saat ini belum diketahui, walaupun demikian, tidak terlihat interaksi yang bermakna jika diberikan bersama *gemcitabine.*

Jangan menggunakan obat lain tanpa memberitahukan dokter atau berkonsultasi dengan apoteker.

11. Apakah Theracim boleh digunakan pada ibu hamil dan menyusui?

Penggunaan Theracim selama kehamilan tidak direkomendasikan. Theracim hanya boleh diberikan pada wanita hamil, ataupun wanita yang tidak menggunakan kontrasepsi secara adekuat jika potensi manfaatnya melebihi risikonya pada janin. Jika pasien hamil selama mendapat obat ini, pasien harus diinformasikan mengenai potensi bahayanya pada janin dan/atau potensi risiko keguguran.

Nimotuzumab dikeluarkan dalam air susu ibu, oleh karena itu, Theracim tidak direkomendasikan untuk digunakan pada ibu menyusui.

12. Apakah boleh mengendarai atau menjalankan mesin selama menggunakan Theracim?

Efek *nimotuzumab* terhadap kemampuan mengendarai atau menggunakan mesin tidak diketahui. Hati-hati jika pasien akan mengendarai atau menggunakan mesin setelah diberikan *nimotuzumab*.

13. Apa efek samping yang mungkin terjadi dengan Theracim?

Efek samping yang sering dilaporkan pada dosis yang direkomendasikan setelah pemberian *nimotuzumab* yang setidaknya mungkin terkait dengan *nimotuzumab* adalah menggigil, lelah, demam tinggi, tremor, muntah, anemia, hipotensi atau hipertensi arteri, demam, peningkatan *alkaline phosphatase*, ALT, dan AST (enzim yang berkaitan dengan fungsi hati), dan sakit kepala.

Dalam uji klinik pada anak, efek samping non-serius yang setidaknya mungkin dipertimbangkan terkait dengan *nimotuzumab* adalah eritema (kemerahan pada kulit), leukopenia (penurunan jumlah sel darah putih), lelah, sakit kepala, mual, dan muntah.

Efek samping yang jarang dilaporkan adalah mialgia (nyeri otot), somnolens (mengantuk), disorientasi (kebingungan dalam hal waktu, tempat, orang, dll), hematuria (ada darah di urin), dan peningkatan enzim fungsi hati.

Dalam pengalaman klinis, reaksi alergi yang berpotensi fatal sangat jarang dilaporkan. Kejadian ini termasuk hipotensi berat dan cepat dan urtikaria (bentol-bentol di kulit/biduran).

Dalam uji klinik fase III pada pasien kanker kepala leher, efek samping yang setidaknya mungkin dipertimbangkan berkaitan dengan *nimotuzumab* dalam kombinasi dengan kemoradioterapi adalah mukositis (sariawan) dan ruam makulopapuler (kemerahan pada kulit berupa bentol kecil/datar). Mukositis dan ruam makulopapuler lebih sering dilaporkan pada kombinasi *nimotuzumab* dengan kemoradioterapi dibandingkan kelompok kemoradioterapi saja. Efek samping lainnya yang dijumpai dengan frekuensi

sebanding pada kelompok kemoradioterapi dan *nimotuzumab* dalam kombinasi dengan kemoradioterapi adalah efek samping hematologi (anemia/penurunan jumlah sel darah merah, neutropenia/penurunan jumlah sel darah putih, demam neutropenia, trombositopenia/penurunan jumlah keping-keping darah), efek samping biokimia (peningkatan kreatinin serum, AST, ALT), gangguan elektrolit (hiponatremia/penurunan kadar natrium, hipokalemia/penurunan kadar kalium, hipomagnesemia/penurunan kadar magnesium), efek samping lokal radiasi (dermatitis radiasi, odinofagia/nyeri saat menelan, disfagia/kesulitan menelan), efek samping saluran cerna (mual, muntah, penurunan berat badan), efek samping lainnya (*stroke*, tinitus/telinga berdenging). Efek samping jangka panjang (> 90 hari) yaitu xerostomia (mulut kering), disgeusia (gangguan pengecapan), fibrosis subkutan (jaringan parut pada kulit), berkurangnya rentang pergerakan, disfagia, gangguan pendengaran karena sensorineural (persarafan), juga sebanding antara 2 kelompok.

Beritahukan dokter Anda jika Anda mendapati apapun yang mengganggu, bahkan jika tidak terdapat dalam daftar efek samping.

14. Apa tanda dan gejala overdosis serta apa yang harus dilakukan jika overdosis?

Pada penelitian di Kanada, dosis sampai dengan 800 mg/minggu pada manusia dilaporkan aman dan ditoleransi dengan baik.
Theracim diberikan di bawah pengawasan dokter, sangat kecil kemungkinannya jika dosis yang diberikan berlebihan. Namun, jika Anda mengalami efek samping apapun setelah diberikan Theracim, segera beritahukan dokter atau perawat Anda.

15. Bagaimana cara menyimpan Theracim?

Theracim harus disimpan pada suhu 2-8°C.

HARUS DENGAN RESEP DOKTER
No. Reg.

Diproduksi oleh:
Center of Molecular Immunology
Havana, Cuba

Diimpor dan dipasarkan oleh:
PT Kalbe Farma Tbk
Bekasi - Indonesia