



腦妥[®] 靜脈輸注液 0.02% W/V
Nimotop[®] Infusion Solution 0.02% W/V

主成份：nimodipine

輸注液

衛署藥輸字第

018843 號

成份

每小瓶五十毫升的輸注液含有十毫克的 nimodipine 溶於五十毫升的含酒精溶劑中。

適應症

預防、治療因動脈瘤引起之蜘蛛膜下出血後，腦血管痙攣所引起的缺血性神經缺損。

劑量及給藥方式《本藥限由醫師使用》

劑量

除非有特殊的處方，一般建議的使用劑量如下：

靜脈輸注：

開始治療時，給予每小時 1 毫克的 nimodipine（等於每小時給予 5 毫升 Nimotop 輸注液）（約等於 15 µg/公斤體重/小時）持續 2 小時。若病人可以忍受上述劑量，且病人的血壓沒有顯著的降低，在兩小時後將劑量調高至每小時給予 2 毫克的 nimodipine（等於每小時給予 10 毫升 Nimotop 輸注液）（約等於 30 µg/公斤體重/小時）。體重小於七十公斤或血壓不穩定的病人的起始劑量為每小時 0.5 毫克的 nimodipine（等於每小時給予 2.5 毫升 Nimotop 輸注液）。

腦內的輸注法：

20 毫升的 Nimotop 稀釋液：將 1 毫升的 Nimotop 輸注液以 19 毫升的林格氏液稀釋。稀釋後的溶液在配製後應立即使用。

若病人發生副作用，則須減低劑量或停止治療。較嚴重的肝功能損害，尤其是肝硬化，可能會因降低首渡效應(first-pass capacity)及減少代謝清除率，而造成 nimodipine 的生體可用率增加，進而使 nimodipine 的作用及副作用，如血壓的降低，皆可能增強。在這些情況下，應依據血壓變化適度地降低劑量；如果可能的話，應考慮停止治療。

給藥方式

Nimotop 輸注液須用輸注幫浦以連續靜脈輸注經由中央導管 (central catheter) 注入體內。Nimotop 輸注液應與下列溶液以一比四的比例經由三向活塞(three-way stopcock)給予，這些溶液包括 5%葡萄糖、0.9% 氯化鈉、乳酸鹽林格氏液(lactated Ringer's solution)、含有鎂的乳酸鹽林格氏液、dextran 40 solution 或 HAES[®](poly(O-2-hydroxyethyl) starch 6%。而甘露醇(mannitol)、人類白蛋白(human albumin)以及血液也適合與 Nimotop 輸注液同時給藥。

Nimotop 輸注液不可加在輸注袋或瓶中，也不可與其他的藥物混合。在麻醉，手術及血管攝影的過程中，皆應持續給予 Nimotop。

三向活塞(three-way stopcock)是用於同時連接 Nimotop 的聚乙烯管、共同輸注液管以及中央導管。

用藥期間

預防性使用：

靜脈輸注治療應該在出血後的四天內開始使用，且在血管收縮危險性最大的期間內應持續使用，即出血後的十至十四天。

如果出血處以手術治療，則預防性使用之 Nimotop 的輸注時間應從手術後至少持續五天。

在靜脈輸注治療結束後，一般建議使用口服 nimodipine 持續治療，一天服用六次 60mg 的 nimodipine，每四小時服用一次，持續七天。

治療性使用：

假如顱內動脈瘤破裂導致蜘蛛膜下腔出血後，因為血管收縮所造成的缺血性神經傷害已經存

在，應及早開始治療，並持續治療至少五天，至多十四天。

在靜脈輸注治療結束之後，一般建議使用口服 nimodipine 持續治療，一天服用六次 60mg 的 nimodipine，每四小時服用一次，持續七天。

若在治療性或預防性給予 Nimotop 的期間，已使用手術處理出血源，則在手術後仍應持續至少五天的 Nimotop 靜脈輸注治療。

腦內的輸注法

在手術進行期間，應使用新鮮配製的 Nimotop 稀釋液（將 1 毫升的 Nimotop 輸注液以 19 毫升的林格氏液稀釋），並將其加溫至與血液同溫，再注入腦內。稀釋後的溶液在配製後應立即使用。

禁忌

Nimotop 輸注液不可使用於對 nimodipine 或其所含任何賦形劑過敏者。

警告和注意事項

雖然目前尚未顯示 nimodipine 治療與顱內壓升高有直接關係，當在這些情況下或腦組織內的水分上升時(統稱腦水腫)建議密切監測顱內壓的變化。

患有低血壓（收縮壓小於 100 mmHg）的病人使用時必須特別注意。

雖然本品包含體積 23.7%的酒精(以 250 毫升每日劑量計算，高達 50 公克)，可能對酒精中毒者或酒精代謝功能不全者是有害的，於懷孕或哺乳婦女、小孩和高危險群(例如肝病或癲癇患者)必須小心使用。

本品中酒精的含量可能會影響其他藥品的作用。

交互作用

影響 nimodipine 作用的藥物:

Fluoxetine

併用 nimodipine 和抗憂鬱藥 Fluoxetine 於穩定狀態時，會導致 nimodipine 血中濃度升高約 50%，而 Fluoxetine 的濃度則明顯地被降低，然而它的活性代謝產物 norfluoxetine 並不受影響。

Nortriptyline

併用 nimodipine 和 nortriptyline 於穩定狀態時，會導致 nimodipine 的濃度少許降低，然而 nortriptyline 的血中濃度不受影響。

受 nimodipine 作用影響的藥物:

降血壓藥

Nimodipine 與降血壓藥併服會增強血壓降低的作用，受影響的降血壓藥如下:

- 利尿劑
- β -阻斷劑
- ACE 抑制劑
- A1-拮抗劑
- 其它鈣離子阻斷劑
- α -腎上腺素阻斷劑
- PDE5 抑制劑
- α -methyldopa

然而，若無法避免同時併用這類藥物，則必須小心監測病患的狀況。

同時靜脈注射 β 阻斷劑可能會造成血壓更顯著的降低，且同時更減弱心臟收縮力而造成無代償性的心衰竭。

若同時併用 潛在 具有腎毒性的藥物 (如: aminoglycosides, cephalosporins, furosemide)，或病患本身的腎功能不佳，則腎功能會變得更差。對於上述的病患，應小心監測其腎功能，若發現病人的腎功能變差，則應該考慮是否停藥。

Zidovudine

在猴子實驗同時併用抗 -HIV 藥物 zidovudine i.v.和 nimodipine bolus i.v. 會導致 zidovudine 有顯著較高的 AUC，然而分佈體積和清除率會明顯的減少。

其它交互作用:

由於 Nimotop 輸注液的組成中含有佔體積 23.7%的酒精，應特別注意與酒精不相容的藥物間之交互作用。

懷孕和哺乳期間的使用

懷孕期

目前並沒有在懷孕婦女 上有足夠 適當 且 控制良好的研究。在懷孕間 如果 必須使用 nimodipine 輸注液時，應該依據臨床狀況仔細評估使用 nimodipine 輸注液的好處以及可能造成的危險性，再決定是否使用。

哺乳期

已知 nimodipine 和其代謝物存在母乳中的濃度與存在母體的血中濃度相同，建議哺乳期的婦女在使用本品時建議不要哺乳給嬰兒。

對駕車及操作機械能之影響

一般而言，駕駛能力及操作機械的能力變差可能與頭暈的發生有關。假如必須使用 Nimotop 輸注液，這樣的影響一般說來不是很重要。

藥物不良反應

嚴重藥物不良反應是依據 nimodipine 用於治療動脈瘤性蜘蛛網膜下腔出血的臨床試驗，以 CIOMS III 發生頻率分類 (安慰組對照試驗: nimodipine 組 N=703;安慰劑組 N=692，無對照組試驗: nimodipine 組 N=2496;至 2005 年 8 月 31 日為止)，如下所列:

發生頻率 ≥ 0.1% 且 <1% (不常見)

血液和淋巴系統

免疫系統

神經系統

心臟疾病

血管疾病

胃腸道疾病

血小板減少

過敏反應、紅疹

頭痛

心跳過速

低血壓、血管舒張

噁心

發生頻率 ≥ 0.01% 且 <0.1% (少見)

心臟疾病

胃腸道疾病

肝膽疾病

一般疾病和注射部位症狀

心搏徐緩

腸阻塞

短暫性肝臟酵素增加

注射和輸注部位的反應、

輸注部位(血栓)靜脈炎

藥物過量

中毒的症狀

可預期的急性藥物過量症狀是血壓顯著地降低，心跳加速或心跳減緩，以及(口服給藥之後)腸胃不適與噁心。

中毒的治療

若急性藥物過量的情況發生，則應立即停止 Nimotop 的治療，應依據症狀給予緊急的治療

措施。如果是口服給藥，緊急的治療措施應為洗胃並給予活性碳。若血壓顯著降低，則可以靜脈注射 **dopamine** 或 **noradrenaline**。由於並沒有已知特定的解毒劑，後續其他副作用的治療則是依據最顯著的症狀加以處理。

藥效學特性

Nimodipine 具有抗腦血管收縮及抗缺血的活性。在體外試驗中，**nimodipine** 可預防或消除各種血管活性的物質（如：血清素，前列腺素，以及組織胺）或血液及血液分解物所引起的血管收縮反應。**nimodipine** 同時也具有神經藥理學及精神藥理學方面的特性。

對於發生急性腦血流病變的病人所進行的研究發現，**nimodipine** 可使腦血管舒張並促進腦部血流的循環。一般來說，在原來受損或血流量不足的部位，增加的血流量會遠比正常的部位要多。

Nimodipine 會顯著地降低蜘蛛膜下腔出血病人因缺血所造成的神經性傷害，並降低致死亡率。

藥動學特性

吸收

口服 **nimodipine** 活性物質幾乎可以完全被人體吸收，在最高試驗劑量下(90 毫克)，血中最高濃度和曲線下面積與劑量間成比例地增加。

靜脈注射時的分佈體積(Vss，二室模式)是 0.9-1.6 l/kg 體重，總(全身)清除率是 0.6-1.9 l/h/kg。

蛋白質結合和分佈

97-99%的 **nimodipine** 會與血漿中的蛋白質結合。

代謝、排除和排泄

Nimodipine 經由 cytochrome P450 3A4 代謝排除。

生體可用率

由於約 85-95%肝臟首渡效應，絕對生體可用率是 5-15%。

臨床前安全性資料

依據單一劑量和重複劑量的毒性、基因毒性、致癌性和男性及女性生殖能力試驗的臨床前資料顯示對人體沒有特別毒性，懷孕大白鼠每天每公斤給予 30 毫克或更高的劑量時，會抑制胎兒生長並導致胎兒體重減少，每天每公斤給予 100 毫克時會發生胎兒致死的可能。目前尚未觀察到致畸胎毒性，在兔子的試驗，每天每公斤給予高達 10 毫克的劑量並無胚胎毒性和致畸胎毒性產生。在一項大白鼠出生至出生後的研究，每天每公斤給予 10 毫克或更高劑量可觀察到致死率和生長遲緩的現象，此發現在隨後的試驗中並未被證實。

配伍禁忌

由於 **Nimotop** 輸注液的有效成份會被聚氯乙烯(PVC)所吸附，所以只能使用聚乙烯(PE)的輸注管。

Nimotop 輸注液的有效成份對光有些許的敏感，應避免直接在日光下使用。如果在輸注過程中無法避免直接暴露在日光下，應使用黑色、棕色、黃色或紅色的玻璃注射器及連接管，或是將輸注幫浦及連接管以不透明材質包裹。然而，若 **Nimotop** 是在漫射的日光或人造光之下給藥，則不需特別的保護措施可達十小時。

操作指南

為了正確地將針頭穿刺入覆蓋的注射瓶塞，建議使用尖細的注射針。禁止使用粗的輸注針頭，因為可能會導致瓶塞破裂或產生凹痕，及瓶塞可能會因為施力過當而掉入注射瓶中。注射用藥於使用前須先經肉眼觀察產品有無異狀或顏色變化，任何使用後殘餘的輸注液不可保留供下次使用。

儲存

藥瓶移出紙盒後，應避免光線直接照射。

Nimotop 輸注液在過期後則不應使用。

應將藥物置於兒童無法觸及之處。

包裝

每小瓶 50 公撮，100 小瓶以下盒裝，瓶裝附輸注器。

製造廠：Bayer HealthCare AG 德國拜耳藥廠

廠 址：D-51368 Leverkusen, Germany

瓶裝附輸注器之供應商：Clinico Infusionstechnik, GmbH & Co, Germany

藥 商：台灣拜耳股份有限公司

地 址：台北市信義路五段 7 號 54 樓

電 話：(02)81011000

網 址：www.bayer-pharma.com.tw

Nimotop Infusion Solution / CCDS4 / TW04 / 062006



Nimotop® Infusion Solution 0.02%W/V

Active substance: nimodipine
Infusion solution

Composition

1 vial of 50 ml infusion solution contains 10 mg nimodipine in 50 ml alcoholic solvent.

Indications

Prophylaxis and treatment of ischaemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorrhage of aneurysmal origin.

Posology and method of administration

Dosage

Unless otherwise prescribed, the following dose guidelines are recommended:

- Intravenous infusion:

At the beginning of treatment 1 mg nimodipine (= 5 ml Nimotop infusion solution/h) for 2 h (about 15 µg/kg body weight/h). If this is well tolerated, and particularly if there is no marked reduction in blood pressure, the dose is increased after 2 h to 2 mg nimodipine (= 10 ml Nimotop infusion solution/h) (about 30 µg /kg body weight/h).

Patients whose bodyweight is appreciably below 70 kg or who have labile blood pressure should be started with a dose of 0.5 mg nimodipine (= 2.5 ml Nimotop infusion solution/h).

- Intracisternal installation:

20 ml of a dilute solution of Nimotop: 1 ml of Nimotop infusion solution and 19 ml of Ringer solution. This dilution must be used immediately after preparation.

In patients who develop adverse reactions the dose should be reduced as necessary or the treatment discontinued. Severely disturbed liver function, particularly liver cirrhosis, may result in an increased bioavailability of Nimodipine due to a decreased first-pass capacity and a reduced metabolic clearance. The effects and side-effects, e.g. reduction in blood-pressure, may be more pronounced. In such cases the dose should if appropriate be reduced, depending on the blood pressure; if necessary, discontinuation of the treatment should be considered.

Method of administration

Nimotop infusion solution is administered as a continuous i.v. infusion via a central catheter using an infusion pump. It should be given via a three-way stopcock together with either glucose 5 %, sodium chloride 0.9 %, lactated Ringer's solution, lactated Ringer's solution with magnesium, dextran 40 solution or HAES® (poly(O-2-hydroxyethyl) starch 6 % in a ratio of about 1:4 (NIMOTOP:co-infusion). Also mannitol, human albumin or blood are suitable for co-infusion.

The three-way stopcock should be used to connect the Nimotop polyethylene tube with the co-infusion line and the central catheter.

Nimotop solution must not be added to an infusion bag or bottle and must not be mixed with other drugs.

Administration of Nimotop should be continued during anaesthesia, surgery and angiography.

Duration of use

- Prophylactic use:

Intravenous therapy should be started no later than 4 days after the haemorrhage and be continued during the period of maximum risk of vasospasm, i.e. up to 10 -14 days after the haemorrhage.

If during prophylactic administration of Nimotop, the source of the haemorrhage is treated surgically, intravenous treatment with Nimotop should be continued post-operatively for at least 5 days.

After the end of the infusion therapy, it is advisable to continue with oral administration of 6 x 60 mg nimodipine daily at 4 h intervals for about a further 7 days.

- Therapeutic use:

If ischemic neurological disturbances caused by vasospasm after aneurysmal subarachnoid haemorrhage are already present, treatment should be started as early as possible and be continued for at least 5 days up to a maximum of 14 days.

Thereafter oral administration of 6 x 60 mg nimodipine per day at 4 h intervals for 7 days is recommended.

If during therapeutic administration or prophylactic administration of Nimotop, the source of the hemorrhage is treated surgically, intravenous treatment with Nimotop should be continued post-operatively for at least 5 days.

Intracisternal Instillation

During surgery a freshly prepared dilute solution of Nimotop (1 ml Nimotop infusion solution and 19 ml Ringer solution) warmed up to blood temperature may be instilled intracisternally. This dilute solution of Nimotop must be used immediately after its preparation.

Contraindications

Nimodipine solution for infusion must not be used in cases of hypersensitivity to nimodipine or to any of the excipients.

Special warnings and special precautions for use

Although treatment with nimodipine has not been shown to be associated with increases in intracranial pressure, close monitoring is recommended in these cases or when the water content of the brain tissue is elevated (generalized cerebral edema).

Caution is required in patients with hypotension (systolic blood pressure lower than 100 mm Hg).

This medicinal product contains 23.7 vol% ethanol (alcohol), i.e. up to 50 g per daily dose (250 ml). This may be harmful for those suffering from alcoholism or impaired alcohol metabolism and should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

The amount of alcohol in this medicinal product may alter the effects of other medicines.

Interactions

Drug that affect nimodipine:

Fluoxetine

The steady-state concomitant administration of nimodipine with the antidepressant fluoxetine led to about 50% higher nimodipine plasma concentrations. Fluoxetine exposure was markedly decreased, while its active metabolite norfluoxetine was not affected.

Nortriptyline

The steady-state concomitant administration of nimodipine and nortriptyline led to a slight decrease in nimodipine exposure with unaffected nortriptyline plasma concentrations.

Effects of nimodipine on other drug:

Blood pressure lowering drugs

Nimodipine may increase the blood pressure lowering effect of concomitant applied anti-hypertensives, such as:

- diuretics,
- β -blockers,
- ACE inhibitors,
- A1-antagonists,
- other calcium antagonists,
- α -adrenergic blocking agents,
- PDE5 inhibitors,
- α -methyldopa.

However, if a combination of this type proves unavoidable particularly careful monitoring of the patient is necessary.

Simultaneous intravenous administration of β -blockers may lead to mutual potentiation of negative inotropic action going as far as decompensated heart failure.

Renal function can deteriorate if potentially nephrotoxic drugs (e.g. aminoglycosides, cephalosporins, furosemide) are given simultaneously, and also in patients whose renal function is already impaired. Renal function must be monitored carefully in such cases, and if a deterioration is found discontinuation of the treatment should be considered.

Zidovudine

In a monkey study simultaneous administration of anti-HIV drug zidovudine i.v. and nimodipine bolus i.v. resulted for zidovudine in significantly higher AUC, whereas the distribution volume and clearance were significantly reduced.

Other forms of interaction:

Since Nimotop infusion solution contains 23.7 % vol-% of alcohol, interactions with alcohol-incompatible drugs should be taken into consideration.

Pregnancy and Lactation

Pregnancy:

There are no adequate and well controlled studies in pregnant women. If nimodipine infusion solution is to be administered during pregnancy, the benefits and the potential risks must therefore be carefully weighted according to the severity of the clinical picture.

Lactation:

Nimodipine and its metabolites have been shown to appear in human milk at concentrations of the same order of magnitude as corresponding maternal plasma concentrations. Nursing mothers are advised not to breastfeed their babies when taking the drug.

Effect on Ability to Drive and Use Machines

In principle the ability to drive and use machines can be impaired in connection with the possible occurrence of dizziness. In case of using Nimotop infusion solution, this influence will generally not be of importance.

Undesirable effects

Adverse drug reactions (ADRs) based on clinical trials with nimodipine in the indication aSAH sorted by CIOMS III categories of frequency (placebo-controlled studies: nimodipine N = 703; placebo N = 692; uncontrolled studies: nimodipine N = 2496; status: 31 Aug 2005) are listed below:

Uncommon $\geq 0.1\%$ to $< 1\%$

Blood and lymphatic system disorders
Immune system disorders

Thrombocytopenia
Allergic reaction, rash

Nervous system disorders
Cardiac disorders
Vascular disorders
Gastrointestinal

Headache
Tachycardia
Hypotension, vasodilatation
Nausea

Rare $\geq 0.01\%$ to $< 0.1\%$

Cardiac disorders
Gastrointestinal disorders
Hepatobiliary disorders
General disorders and administration site conditions

Bradycardia
Ileus
Transient increase in liver enzyme
Injection and infusion site reactions,
infusion site (thrombo-)phlebitis

Overdose

Symptoms of intoxication

Symptoms of acute overdosage to be anticipated are marked lowering of the blood pressure, tachycardia or bradycardia, and (after oral administration) gastrointestinal complaints and nausea.

Treatment of intoxication

In the event of acute overdosage treatment with Nimotop must be discontinued immediately. Emergency measures should be governed by the symptoms. If the substance was ingested orally, gastric lavage with addition of charcoal should be considered as an emergency therapeutic measure. If there is a marked fall in blood pressure, dopamine or noradrenaline can be administered intravenously. Since no specific antidote is known, subsequent treatment for other side effects should be governed by the most prominent symptoms.

Pharmacodynamic properties

Nimodipine has a predilective cerebral anti-vasoconstrictive and anti-ischemic activity. Vasoconstrictions provoked in vitro by various vasoactive substances (e.g. serotonin, prostaglandins, and histamine) or by blood and blood degradation products can be prevented or eliminated by nimodipine. Nimodipine also has neuropharmacological and psychopharmacological properties.

Investigations in patients with acute cerebral blood flow disturbances have shown that nimodipine dilates the cerebral blood vessels and promotes cerebral blood flow. The increase in perfusion is as a rule greater in previously damaged or underperfused brain region than in healthy regions.

The ischemic neurological damage in patients with subarachnoid hemorrhage and the mortality rate are significantly reduced by nimodipine.

Pharmacokinetic Properties

Absorption

The orally administered active substance nimodipine is practically completely absorbed. The peak plasma concentration and the area under the curve increase proportionally to the dose up to the highest dose under test (90 mg).

The distribution volume (V_{ss} , 2-compartment model) for i.v. administration is calculated to be 0.9 - 1.6 l/kg body weight. The total (systemic) clearance is 0.6 - 1.9 l/h/kg.

Protein binding and distribution

Nimodipine is 97 - 99 % bound to plasma proteins.

Metabolism, elimination and excretion

Nimodipine is eliminated metabolically via the cytochrome P450 3A4 system.

Bioavailability

Attributed to the extensive first-pass metabolism (about 85 - 95 %) the absolute bioavailability is 5 - 15 %.

Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenicity and male and female fertility. In pregnant rats, doses of 30 mg/kg/day and higher inhibited foetal growth and resulted in reduced foetal weights. At 100 mg/kg/day embryoletality occurred. No evidence of teratogenicity was observed. In rabbits, no embryotoxicity and teratogenicity occurred at doses up to 10 mg/kg/day. In one peri-postnatal study in rats, mortality and delayed physical development were observed at doses of 10 mg/kg/day and higher. The findings were not confirmed in subsequent studies.

Incompatibilities

Since the active substance of Nimotop infusion solution is absorbed by polyvinyl-chloride (PVC), only polyethylene (PE) infusion tubing may be used.

The active substance of Nimotop infusion solution is slightly light-sensitive such that its use in direct sunlight should be avoided. If direct exposure to sunlight is unavoidable during an infusion, black, brown, yellow or red glass syringes and connecting tubing should be used, or the infusion pump and the tubing be protected by opaque wrappings. However, no special protective measures need be taken for up to 10 h if Nimotop is being given in diffuse daylight or in artificial light.

Instructions for use/handling

To penetrate the coated injection stoppers correctly, fine acute injection needles are recommended. Do not use large-core infusion needles, since this may result in cracked or bruised stoppers and the stoppers may be forced into the vial.

Parenteral drug products should be inspected visually for particulate matter and color change prior to administration. Any residual solution should not be kept for later use.

Special precautions for storage

Protect from direct sunlight, if the bottle is removed from the carton.
Nimotop infusion solution must not be used after the expiry date.

Keep drugs out of reach of children.

Presentation

50 ml per vial, below 100 vials per box, vial with IV set.

Bayer HealthCare AG, D-51368 Leverkusen, Germany
IV set: Clinico Infusionstechnik, GmbH & Co, Germany
Nimotop Infusion Solution / CCDS4 / TW04 / 062006