



# 腦妥<sup>®</sup> 膜衣錠30毫克 Nimotop<sup>®</sup> F. C. Tablets 30mg

衛署藥輸字第018842號

<b>藥品名稱</b>
腦妥 <sup>®</sup> 膜衣錠30毫克
<b>成份含量</b>
每一錠腦妥 <sup>®</sup> 膜衣錠含30毫克的nimodipine。
<b>劑型</b>
膜衣錠
<b>臨床特性</b>
<b>適應症</b>
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。
<b>用法用量</b> 《本藥須由醫師處方使用》
Nimotop靜脈輸注液輸注5 - 14天後，建議再口服Nimotop膜衣錠7天。一般而言，錠劑應整顆以水吞服，不需隨餐服用。禁止與葡萄柚汁併服。(請參閱“藥物交互作用和其他型式的交互作用”)每次用藥的間隔時間不可少於四小時。口服Nimotop膜衣錠是隨著Nimotop靜脈輸注液治療後使用。

**劑量**  
除非有特殊的處方，一般建議的使用劑量如下：建議用法是先以Nimotop靜脈輸注液輸注5 - 14天，接著再改以每天口服六次、每次兩錠Nimotop膜衣錠(6 x 60 mg nimodipine)。若病人發生副作用，則須減低劑量或停止治療。與CYP3A4抑制劑或CYP3A4誘導劑併用時，可能須調整劑量。(請參閱“藥物交互作用和其他型式的交互作用”)

- 預防性使用  
靜脈輸注治療結束後，建議使用口服Nimotop膜衣錠持續治療，一天服用六次60mg的Nimotop膜衣錠，每四小時服用一次，持續七天。

- 治療性使用  
靜脈輸注治療後，建議使用口服Nimotop膜衣錠持續治療，一天服用六次60mg的Nimotop膜衣錠，每四小時服用一次，持續七天。

**肝功能不全的病患**  
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；必要時，應考慮停止治療。

**禁忌**  
本品不可使用於對nimodipine或其所含任何賦形劑過敏者。併用nimodipine與rifampicin是禁忌，因為rifampicin會明顯減低nimodipine的療效(“藥物交互作用和其他型式的交互作用”)。同時口服nimodipine和抗癲癇藥物phenobarbital、phenytoin和carbamazepine是禁忌，因為會明顯降低nimodipine的療效(請參閱“藥物交互作用和其他型式的交互作用”)。

**警語及注意事項**  
雖然目前尚未顯示nimodipine治療與顱內壓升高有直接關係。當在前述病例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。有不規律心絞痛或在4週內發生心肌梗塞的病患，醫生應衡量可能造成的危險性(例如：冠狀動脈灌注減少與心肌缺血)與效益(例如：腦灌注的改善)。Nimodipine經由cytochrome P450 3A4系統代謝，已知會抑制或誘發這酵素系統的藥物均會改變nimodipine的首渡效應或清除率(請參閱“藥物交互作用和其他型式的交互作用”)。已知cytochrome P450 3A4系統抑制劑，可能會導致nimodipine血中濃度上升的藥物，如下：
- 巨環類抗生素 (例如：erythromycin)
- 抗HIV蛋白酶抑制劑 (例如：ritonavir)
- Azole antimycotics (例如：ketoconazole)
- 抗憂鬱劑：nefazodone和fluoxetine
- quinupristin/dalfopristin
- cimetidine
- valproic acid
併用上述藥品時必須小心監控血壓，必要時，須考慮減少nimodipine的劑量。

**藥物交互作用和其他型式的交互作用**  
影響nimodipine的藥物：Nimodipin是經由位在小腸粘膜及肝臟的cytochrome P450 3A4系統代謝，藥物不論是抑制或誘發這酵素系統者均會改變nimodipine的首渡效應或清除率。

當nimodipine與下列藥物併用時，須考慮藥物間交互作用的持續時間和程度：

**Rifampicin**  
從使用其他鈣離子拮抗劑的經驗得知，由於rifampicin有誘導酵素的作用，預期會加速Nimodipine的代謝。所以當同時服用rifampicin時，會明顯降低nimodipine的療效，所以併用nimodipine和rifampicin是禁忌(請參閱“禁忌”)。

**誘導cytochrome P450 3A4系統的抗癲癇藥物，例如：Phenobarbital、phenytoin或carbamazepine**  
長期使用抗癲癇藥物phenobarbital、phenytoin或carbamazepine會明顯地降低口服nimodipine的生體可用率，因此同時口服nimodipine和上述抗癲癇藥是禁忌(請參閱“禁忌”)。

併用下列cytochrome P450 3A4系統抑制劑須小心監控血壓，必要時，須調整nimodipine的劑量(請參閱“用法用量”)。

**巨環類抗生素 (例如erythromycin)**  
目前並沒有nimodipine和巨環類抗生素間交互作用的研究。但因某些巨環類抗生素已知具有cytochrome P450 3A4系統抑制的作用，所以無法排除潛在藥物間的交互作用，因此巨環類抗生素不應該與nimodipine併用(請參閱“警告及注意事項”)。雖然azithromycin結構上與巨環類抗生素相似，但是不具CYP3A4抑制的作用。

**抗HIV蛋白酶抑制劑 (例如：ritonavir)**  
目前尚無正式的試驗，研究nimodipine和抗HIV蛋白酶抑制劑間潛在的交互作用。但抗HIV蛋白酶抑制劑已被報導是cytochrome P450 3A4系統的強力抑制劑，因此無法排除併用這些蛋白酶抑制劑導致臨床上nimodipine血中濃度顯著增加的可能(請參閱“警語及注意事項”)。

**Azole anti-mycotics (例如： ketoconazole)**  
目前尚無正式的試驗，研究nimodipine和ketoconazole間潛在的交互作用。但已知Azole anti-mycotics會抑制cytochrome P450 3A4系統，而且與其他dihydropyridine類鈣離子拮抗劑的各種交互作用已經被報導，因此當與口服nimodipine併用時，不能排除因為首渡效應減低而導致nimodipine全身性生體可用率增加的可能 (請參閱“警語及注意事項”)。

**Nefazodone**  
目前尚無正式的試驗，研究nimodipine和nefazodone間潛在的交互作用。但抗憂鬱藥已被報導是cytochrome P450 3A4強力抑制劑，因此不可排除因為併用nefazodone而導致nimodipine血中濃度增加的可能(請參閱“警語及注意事項”)。

**Fluoxetine**  
同時服用nimodipine和抗憂鬱藥fluoxetine會導致nimodipine穩定狀態血中濃度升高50%，Fluoxetine的暴露量則明顯降低，然而其活性代謝物norfluoxetine不受影響。

**Quinupristin/dalfopristin**  
依據鈣離拮抗劑nifedipine的經驗，併用quinupristin/dalfopristin可能會導致nimodipine血中濃度增加(請參閱“警語及注意事項”)。

**Cimetidine**  
同時使用H2拮抗劑cimetidine會導致nimodipine血中濃度增加(請參閱“警語及注意事項”)。

**Valproic acid**  
同時使用抗癲癇藥valproic acid會導致nimodipine血中濃度增加(請參閱“警語及注意事項”)。

**其他藥物交互作用：**  
**Nortryptiline**  
同時使用nimodipine和nortryptiline會導致穩定狀態nimodipine暴露量稍微降低，然而不影響nortryptiline的血中濃度。

Nimodipine對其他藥物的影響：
**降血壓藥**  
Nimodipine可能會增加併用之抗高血壓藥物的降血壓作用，例如：
- 利尿劑
- β-阻斷劑
- ACE抑制劑
- A1拮抗劑
- 其他鈣離子阻斷劑
- α-交感神經阻斷劑
- PDE5抑制劑
- α-methyl dopa

然而，若無法避免同時併用這類藥物時，則必須小心監測病患的狀況。

**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，而分佈體積和清除率則是明顯的減少。

**藥物與食物間的交互作用：**  
**葡萄柚汁**  
葡萄柚汁會抑制cytochrome P450 3A4系統，同時服用dyhydropyridine類鈣離子拮抗劑和葡萄柚汁，由於首渡效應降低或清除率減少會導致nimodipine血中濃度升高和作用延長。結果會增強降血壓的作用，攝取葡萄柚汁後此作用將持續至少4天。所以當服用nimodipine時應避免攝取葡萄柚/葡萄柚汁 (請參閱“用法用量”)。

**懷孕和哺乳**  
**懷孕**  
目前並沒有在懷孕婦女上有足夠適當且控制良好的研究。在懷孕期間如果必須使用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**  
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似，建議哺乳期的婦女在使用本品時建議不要哺乳給嬰兒。

**生殖能力**  
在一個體外授精的案例中，鈣離子拮抗劑與精子頭部的可逆性生物化學變化有直接關係，也許這會造成精子功能損傷。

**對於駕駛或操作機械能力的影響**  
一般而言，駕駛能力及操作機械的能力會變差，此可能與頭暈的發生有關。

**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：

Nimodipinen 藥品不良反應的發生頻率列於下表中。在每一發生頻率分類中，不良反應依據嚴重程度遞減排列。

**發生頻率的定義：**  
很常見 (≥ 1/10),  
常見 (≥ 1/100 to < 1/10),  
不常見 (≥ 1/1,000 to < 1/100),  
少見 (≥ 1/10,000 to < 1/1,000),  
罕見 (< 1/10,000).

System Organ Class (MedDRA)	不常見	少見
<b>血液和淋巴系統</b>	<b>血小板減少</b>	
<b>免疫系統</b>	<b>過敏反應</b>	
	<b>紅疹</b>	
<b>神經系統</b>	<b>頭痛</b>	
<b>心臟疾病</b>	<b>心跳過速</b>	<b>心博徐緩</b>
<b>血管疾病</b>	<b>低血壓</b>	
	<b>血管舒張</b>	
<b>胃腸道疾病</b>	<b>噁心</b>	<b>腸阻塞</b>
<b>肝膽疾病</b>		<b>短暫性肝臟酵素增加</b>

**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膜衣錠的治療，應依據症狀給予緊急的治療措施。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**  
**藥學學特性**  
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呈現線性比例。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0.6-1.99 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毫克時則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生長遲緩乃至死亡的現象，但此發現在隨後的試驗中並未被證實。

**藥劑特性**  
**賦形劑**  
Poly(1-vinyl-2-pyrrolidone) 25, microcrystalline cellulose, corn starch, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, macrogol 4000, titanium dioxide (E 171), iron oxide yellow (E 172).

**注意**  
Nimotop膜衣錠在過期後不可使用。應將藥物置於兒童無法觸及之處。

**包裝**  
20 - 1000錠盒裝及鋁箔包裝。

製造廠：Bayer Schering Pharma AG  
廠 址：D-51368 Leverkusen, Germany  
藥 商：台湾拜耳股份有限公司  
地 址：台北市信義路五段7號54樓  
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Nimotop F.C. Tablets 30mg / CDS5 / TW05 / 092011

**Bayer**

Bayer Schering Pharma





# Nimotop® F. C. Tablets 30 mg

Active substance: nimodipine

Film-coated tablet

## Name OF THE MEDICINAL PRODUCT

Nimotop® F. C. Tablets 30mg

## COMPOSITION

1 Nimotop tablet 30 mg contains 30mg nimodipine.

## PHARMACEUTICAL FORM

Film-coated tablet

## CLINICAL PARTICULARS

### Indications

After a preceding infusion of Nimotop infusion solution, for the prophylaxis and treatment of ischaemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorrhage of aneurysmal origin.

### Dosage and method of administration

Administration of Nimotop tablets is recommended for about 7 days after the end of the 5-14 days infusion therapy with Nimotop infusion solution.

In general, the tablets should be swallowed whole with a little liquid, independent of meal time. Grapefruit juice is to be avoided (*see "Interaction with other medicinal products and other forms of interaction"*).

The interval between successive doses must not be less than 4 h.

Nimotop tablets are indicated subsequently to Nimotop infusion solution.

### Dosage regimen

Unless otherwise prescribed, the following dose guidelines are recommended:

The recommended procedure is administration of Nimotop infusion solution for 5-14 days, followed by a daily dose of 6 x 2 Nimotop film-coated tablets (6 x 60 mg nimodipine).

In patients who develop adverse reactions the dose should be reduced as necessary or the treatment discontinued.

Upon co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers a dose-adaption may be necessary (*see "Interaction with other medicinal products and other forms of interaction"*).

### Prophylactic Use:

After the end of the infusion therapy, it is advisable to continue with oral administration of 6 x 60 mg Nimotop tablets daily at four-hourly intervals for about further 7 days.

### Therapeutic Use:

After intravenous application, oral administration of 6 x 60 mg Nimotop tablet per day at four-hourly intervals for 7 days is recommended.

### Patients with hepatic impairment

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 these patients.

In such cases the dose should be reduced or, if necessary, discontinuation of the treatment should be considered.

## CONTRAINDICATIONS

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

The use of nimodipine in combination with rifampicin is contraindicated as efficacy of nimodipine tablets could be significantly reduced when concomitantly administered with rifampicin. (*see "Interaction with other medicinal products and other forms of interaction"*).

The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin or carbamazepine is contraindicated as efficacy of nimodipine tablets could be significantly reduced. (*see "Interaction with other medicinal products and other forms of interaction"*).

## SPECIAL WARNINGS AND 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).

In patients with unstable angina or within the first 4 weeks after acute myocardial infarction, physicians should consider the potential risk (e.g. reduced coronary artery perfusion and myocardial ischemia) versus the benefit (e.g. improvement of brain perfusion).

Nimodipine is metabolized via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nimodipine. (*see "Interaction with other medicinal products and other forms of interaction"*).

Drugs, which are known inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nimodipine are, e.g.:

- macrolide antibiotics (e.g., erythromycin),
- anti-HIV protease inhibitors (e.g., ritonavir),
- azole antimycotics (e.g., ketoconazole),
- the antidepressants nefazodone and fluoxetine
- quinupristin/dalfopristin,
- cimetidine,
- valproic acid.

Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nimodipine dose should be considered.

## INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

### Drugs that affect nimodipine:

Nimodipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nimodipine.

The extent as well the duration of interactions should be taken into account when administration nimodipine together with the following drugs:

### Rifampicin

From the experience with the other calcium antagonists it has to be expected that rifampicin accelerates the metabolism of nimodipine due to enzyme induction. Thus, efficacy of nimodipine could be significantly reduced when concomitantly administered with rifampicin. The use of nimodipine in combination with rifampicin is therefore contraindicated (*see "Contraindications"*).

### Cytochrome P450 3A4 system-inducing anti-epileptic drugs, such as phenobarbital, phenytoin or carbamazepine

Previous chronic administration of the antiepileptic drugs phenobarbital, phenytoin or carbamazepine markedly reduces the bioavailability of orally administered nimodipine. Therefore, the concomitant use of oral nimodipine and these antiepileptic drugs is contraindicated (*see "Contraindications"*).

Upon co-administration with the following inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, an adaptation in the nimodipine dose should be considered (*see "Posology and method of administration"*).

### Macrolide antibiotics (e.g., erythromycin)

No interaction studies have been carried out between nimodipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 system and the potential for drug interaction cannot be ruled out at this stage. Therefore, macrolide antibiotics should not be used in combination with nimodipine (*see "Special warnings and precautions for use"*).

Azithromycin, although structurally related to the class of macrolide antibiotic is void of CYP3A4 inhibition.

### Anti-HIV protease inhibitors (e.g., ritonavir)

No formal studies have been performed to investigate the potential interaction between nimodipine and anti-HIV protease inhibitors. Drugs of this class have been reported to be potent inhibitors of the cytochrome P450 3A4 system. Therefore, the potential for a marked and clinically relevant increase in nimodipine plasma concentrations upon co-administration with these protease inhibitors cannot be excluded (*see "Special warnings and precautions for use"*).

### Azole anti-mycotics (e.g., ketoconazole)

A formal interaction study investigating the potential of drug interaction between nimodipine and ketoconazole has not been performed. Azole anti-mycotics are known to inhibit the cytochrome P450 3A4 system, and various interactions have been reported for other dihydropyridine calcium antagonists. Therefore, when administered together with oral nimodipine, a substantial increase in systemic bioavailability of nimodipine due to a decreased first-pass metabolism cannot be excluded (*see "Special warnings and precautions for use"*).

### Nefazodone

No formal studies have been performed to investigate the potential interaction between nimodipine and nefazodone. This antidepressant drug has been reported to be a potent inhibitor of the cytochrome P450 3A4. Therefore, the potential for an increase in nimodipine plasma concentrations upon co-administration with nefazodone cannot be excluded (*see "Special warnings and precautions for use"*).

### 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.

### Quinupristin/dalfopristin

Based on experience with the calcium-antagonist nifedipine, co-administration of quinupristin/ dalfopristin may lead to increased plasma concentrations of nimodipine (*see "Special warnings and precautions for use"*).

### Cimetidine

The simultaneous administration of the H2-antagonist cimetidine can lead to an increase in the plasma nimodipine concentration (*see "Special warnings and precautions for use"*).

### Valproic acid

The simultaneous administration of the anticonvulsant valproic acid can lead to an increase in the plasma nimodipine concentration (*see "Special warnings and precautions for use"*).

## Further drug interaction:

### Nortryptiline

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

## Effects of nimodipine on other drugs:

### Blood pressure lowering drugs

Nimodipine may increase the blood pressure lowering effect of concomitantly 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.

### 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.

## Drug-food interactions:

### Grapefruit juice

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of dihydropyridine calcium antagonists together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nimodipine due to a decreased first pass metabolism or reduced clearance.

As a consequence, the blood pressure lowering effect may be increased. After intake of grapefruit juice this effect may last for at least 4 days after the last ingestion of grapefruit juice.

Ingestion of grapefruit / grapefruit juice is therefore to be avoided while taking nimodipine (*see "Posology and method for administration"*).

## PREGNANCY AND LACTATION

### Pregnancy

There are no adequate and well controlled studies in pregnant women. If nimodipine 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.

### Fertility

In single cases of in-vitro fertilization calcium antagonists have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function.

## UNDESIRABLE EFFECTS

### Tabulated list of adverse reactions

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:

The frequencies of ADRs reported with nimodipine are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:

very common ( ≥ 1/10),  
common ( ≥ 1/100 to < 1/10),  
uncommon ( ≥ 1/1,000 to < 1/100),  
rare ( ≥ 1/10,000 to < 1/1,000),  
very rare ( < 1/10,000).

### ADR table

	System Organ Class (MedDRA)	Uncommon	Rare
	Blood and the lymphatic system disorders Immune system disorders	Thrombocytopenia Allergic reaction Rash	
	Nervous system disorders Cardiac disorders Vascular disorders	Headache Tachycardia Hypotension Vasodilatation	Bradycardia
	Gastrointestinal disorders Hepato-biliary disorders	Nausea	Ileus Transient increase in liver enzymes

## OVERDOSE

### Symptoms of intoxication

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

### Treatment of intoxication

In the event of acute overdosage treatment with Nimotop tablet must be discontinued immediately. Emergency measures should be governed by the symptoms. 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.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamic properties

Nimodipine has a predilective cerebral anti-vasoconstrictive and anti-ischaemic 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 (Vss, 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.

## PHARMACEUTICAL PARTICULARS

### List of excipients

Poly (1-vinyl-2-pyrrolidone) 25, microcrystalline cellulose, corn starch, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, macrogol 4000, titanium dioxide (E 171), iron oxide yellow (E 172).

### Instructions for use/handling

Nimotop film-coated tablets must not be used after the expiry date.

### Keep drugs out of reach of children.

## PRESENTATION

20 - 1000's per box.

Bayer Schering Pharma AG, D-51368 Leverkusen, Germany  
Nimotop film-coated tablet 30mg / CCDS5 / TW05 / 092011

Bayer

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