NIMOTOP®

Film Coated Tablet

Important information, please read carefully!

Composition

1 film-coated tablet contains 30 mg nimodipine.

Yellow film-coated tablet, round biconvex, diameter 10 mm, radius of curvature 15 mm, weight 339mg, tablet code : one side-SK, other side Bayer Cross.

Properties

PHARMACODYNAMIC PROPERTIES
Nimodipine has a predilective cerebral antivasoconstrictive and antiischaemic 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 ischaemic neurological damage in patients with subarachnoid haemorrhage 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 embryolethality 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.

Therapeutic indications

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

Dosage and method of administration

Dosage:
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 tablets (6 x 60 mg nimodipine).
In patients who develop adverse reactions the dose should be reduced as necessary or the treatment discontinued.

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, depending on the blood pressure; or, if necessary, discontinuation of the treatment should be considered.

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

Administration
Administration of Nimotop tablets is recommended for about 7 days after the end of 5-14 days infusion therapy with Nimotop infusion solution.
In general, the tablets should be swallowed in 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.

Duration of use
Prophylactic Use
After the end of the infusion therapy, it is advisable to continue with oral administration of 6 x 60 mg nimodipine daily at four-hourly intervals for about a further 7 days.

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

Contraindications

Nimotop 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 Nimotop 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 Nimotop tablets could be significantly reduced (see " Interaction with other medicinal products and other forms of interaction ").

Special warnings and special precautions for use

Although treatment with Nimotop 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 oedema).
Caution is required in markedly hypotensive patients (systolic blood pressure < 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.

Interaction 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 administering nimodipine together with the following drugs:

Rifampicin
From the experience with 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”).

Macrolid antibiotics (e.g., erythromycin)
No interaction studies have been carried out between nimodipine and macrolid antibiotics. Certain macrolid 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 macrolid 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”).

Fluoxitine
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 interactions:
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 drugs:
Blood pressure lowering drugs
Nimodipine may increase the blood pressure lowering effect of concomitantly applied anti-hypertensives, such as:

- diuretics,
- ß-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 dyhydropyridine 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 & 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 weighed 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.

In-vitro fertilization
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.

Effects on ability to drive and use machines

In principle the ability to drive and use machines can be impaired in connection with the possible occurence of dizziness.

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:
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).

Table 01: ADR table

System Organ Class (MedDRA)	Uncommon	Rare
Blood and the lymphatic system disorders	Thrombocytopenia	
Immune system disorders	Allergic reaction	
	Rash	
Nervous system disorders	Headache	
Cardiac disorders	Tachycardia	Bradycardia
Vascular disorders	Hypotension	
	Vasodilatation	
Gastrointestinal disorders	Nausea	Ileus
Hepato-biliary disorders		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.
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 nor-adrenaline can be administered intravenously.
Since no specific antidote is known, subsequent treatment for other side effects should be aimed at the most prominent symptoms.

Presentation

Box, 5 strips @ 10 film-coated tablet

Excipients

Microcrystalline celullose, Povidone, Maize starch, Crospovidone, Magnesium stearate, Hypromellose, Macrogol 4000, Titanium dioxide and Iron oxide yellow.

Instruction for use/handling :

Storage
Store below 30°C
Nimotop® film-coated tablet must not be used after the expiry date

Keep the drug out of reach of children

Harus dengan resep dokter

Reg. No. XXXXXXXXXXXXXX

Made by Bayer AG, Leverkusen – Germany
Imported by PT Bayer Indonesia, Depok – Indonesia

Packed by PT Actavis Indonesia, Jakarta – Indonesia