SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

Nimotop tablets 30 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 Nimotop tablet 30 mg contains 30 mg nimodipine.

PHARMACEUTICAL FORM

Film-coated tablet

CLINICAL PARTICULARS

Indication(s)

Prophylaxis and treatment of ischemic neurological deficits caused by cerebral vasospasms following subarachnoid hemorrhage of aneurysmal origin. Nimotop tablets are indicated subsequently to Nimotop infusion solution.

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 individual doses should be not less than four hours.

Dosage regimen

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.
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").

<u>Prophylactic Use:</u>
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.

<u>Therapeutic Use:</u>
After intravenous application, oral administration of 6 x 60 mg Nimotop tablet per day at fourhourly 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

Nimotop tablet must not be administered in case of hypersensitivity to the active substance or to any of the excipients.

The use of nimodipine in combination with rifampicin is contraindicated as efficacy of Nimotop tablet could be significantly reduced when concomitantly administered with rifampicin.

The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin or carbamazepine is contraindicated as efficacy of Nimotop tablet could be significantly reduced.

Treatment of ischaemic neurological deficits (in addition for IBFO):

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.

Therefore, Nimotop tablet must not be administered for treatment of ischemic neurological deficits to patients with severely impaired liver function (e.g. cirrhosis of the liver).

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

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 metabolized 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 .

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. 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 .

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 .

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 .

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.

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 .

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 .

Cimetidine

The simultaneous administration of the H2-antagonist cimetidine can lead to an increase in the plasma nimodipine concentration.

Valproic acid

The simultaneous administration of the anticonvulsant valproic acid can lead to an increase in the plasma nimodipine concentration .

Further drug interaction:

Nortryptyline

The steady-state concomitant administration of nimodipine and nortryptyline led to a slight decrease in nimodipine exposure with unaffected nortryptyline 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 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)*.

Interactions shown not to exist:

Haloperidol

The concurrent steady-state administration of nimodipine in patients on individual long-term haloperidol treatment did not indicate any potential for mutual interaction.

Concomitant administration of oral nimodipine and diazepam, digoxin, glibenclamide, indomethacin, ranitidine, and warfarin did not reveal any potential for mutual interaction.

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.

Effects on ability to drive or use machines

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 aSAH and IBFO are summarized in the tables 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 aSAH

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
Hepatobiliary disorders		Transient increase in liver enzymes

Adverse drug reactions (ADRs) based on clinical trials with **nimodipine in the indication IBFO** sorted by CIOMS III categories of frequency (placebo-controlled studies: nimodipine N = 1,594; placebo N = 1,558; uncontrolled studies: nimodipine N = 8,049; status: 20 Oct 2005) and post marketing reports (status: Oct 2005) are listed below. ADRs listed under "common" were observed with a frequency below 2%.

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:

common ($\geq$ 1/100 to < 1/10),
uncommon ($\geq$ 1/1,000 to < 1/100),
rare ($\geq$ 1/10,000 to < 1/1,000),
very rare (< 1/10,000).

Table 02: ADR table IBFO

System Organ Class (MedDRA)	Common	Uncommon
Immune system disorders		Allergic reaction
		Rash
Nervous system disorders		Headache
		Vertigo
		Dizziness
		Hyperkinesia
		Tremor
Cardiac disorders		Palpitation
		Tachycardia
Vascular disorders	Hypotension	Syncope
	Vasodilatation	Oedema
Gastrointestinal disorders		Constipation
		Diarrhea
		Flatulence

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

ATC code (aSAH) :C08 CA06

ATC code (IBFO) :NO6 DX18

Nimodipine is a calcium antagonist belonging to the 1,4-dihydropyridine group.

Due to its marked lipophilicity, nimodipine crosses the brain barrier easily. In animal studies, nimodipine bound with great affinity and selectivity to the L-type Ca^{++} channels, thus blocking the intracellular flow of calcium through the membrane.

In pathological conditions associated with an increase in intracytoplasmic influx of calcium into nerve cells, for example in the course of cerebral ischaemia, it is considered that nimodipine improves the stability and functional capacity of these cell elements.

Selective blockade of the calcium channels in some areas of the brain, such as the hippocampus and the cortex, may perhaps explain the positive effect of nimodipine on learning and memory deficits observed in various animal models.

The same molecular mechanism probably underlies the vasodilator effect in the brain and the promotion of blood flow by nimodipine observed in animals and man.

Nimodipine has a marked selectivity of action in some cerebral areas. Its therapeutic properties are related to its ability to inhibit the contraction of smooth muscle cells induced by calcium ions.

Nimodipine protects the neurones and stabilises their function; it promotes cerebral blood flow and increases tolerance to ischaemia through interactions with the neuronal and cerebrovascular receptors linked to the calcium channels.

Other studies have shown that this does not result in steal phenomena.

It has been demonstrated clinically that nimodipine improves disorders of memory and concentration in patients with impaired cerebral function.

Other typical symptoms are also influenced favourably, as has been demonstrated by evaluation of the global clinical impression, evaluation of individual disorders, observation of behaviour and psychometric tests

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

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.

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).

Incompatibilities

None

Special precautions for storage

Do not store above 30°C

Keep out of reach of children

Protect from sunlight

Nature and contents of container

Alu/Alu Blister packs; 10 x 10 tablets

Instructions for use / handling

None

On Prescription only

Manufacturer

Bayer AG

51368 Leverkusen

Germany

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