

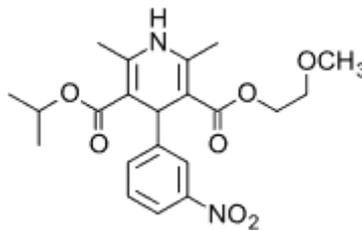
PRODUCT INFORMATION

NIMOTOP®

nimodipine

NAME OF THE MEDICINE

Nimodipine belongs to the class of pharmacological agents known as calcium channel blockers. Nimodipine is isopropyl (2 - methoxyethyl) 1, 4 - dihydro - 2, 6 - dimethyl - 4 - (3 - nitrophenyl) - 3, 5 - pyridine - dicarboxylate. It is a racemic mixture with a molecular weight of 418.5 and a molecular formula of $C_{21}H_{26}N_2O_7$. The CAS Registry Number is: 66085-59-4. The structural formula is:



DESCRIPTION

Nimodipine is a yellow crystalline substance, practically insoluble in water.

Nimodipine is light sensitive but to a much lesser degree than nifedipine.

Nimotop is available as tablets containing 30 mg nimodipine or a 0.2 mg/mL concentrated intravenous infusion solution. Nimotop tablets contain microcrystalline cellulose, povidone, maize starch, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide and iron oxide yellow as excipients. Nimotop concentrated intravenous infusion solution contains ethanol 96% (200 mg/mL), macrogol 400, sodium citrate dihydrate, citric acid and water for injections as excipients.

PHARMACOLOGY

Nimodipine is a calcium channel blocking agent belonging to the 1,4-dihydropyridine group. The mechanism(s) of nimodipine's clinical benefit in patients with subarachnoid haemorrhage has not been fully elucidated. Current evidence suggests that it may have a preferential cerebral vasodilator action and/or a direct effect involving prevention of calcium overload in neurons. It dilates the small resistance cerebral vessels and increases the cerebral blood flow, the increased perfusion being generally more pronounced in brain regions with preliminary damage and restricted circulation than in healthy regions. The improvement in cerebral circulation is particularly evident in patients with cerebral vasospasm after subarachnoid haemorrhage, particularly in Hunt & Hess grades I-III patients (refer to table below). Nimodipine produces significant reductions in ischaemic neurological deficits caused by vasospasm and in mortality.

Assessment of patients with subarachnoid haemorrhage (Hunt & Hess):

Grade 1	Asymptomatic or minimal headache and slight nuchal rigidity
Grade II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
Grade III	Drowsiness, confusion or mild focal deficit
Grade IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
Grade V	Deep coma, decerebrate rigidity, moribund appearance

The contractile processes of the cerebral arterial smooth muscle cells are dependent upon calcium ions, which enter these cells during depolarisation as slow ionic transmembrane currents. Nimodipine binds to specific receptor sites in the central nervous system. It inhibits calcium ion transfer into these cells and inhibits contractions of vascular smooth muscle.

In animal experiments, nimodipine had a greater effect on cerebral arteries than on arteries elsewhere in the body. It is highly lipophilic, allowing it to cross the blood-brain barrier; concentrations of nimodipine as high as 12.5 ng/mL have been detected in the cerebrospinal fluid of nimodipine treated subarachnoid haemorrhage (SAH) patients.

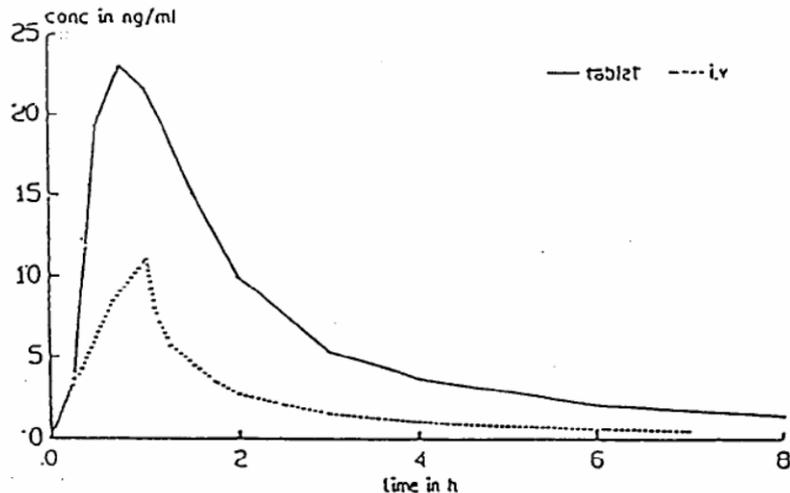
Based on animal experiments, it was hoped that nimodipine would prevent cerebral arterial spasm in SAH patients. While clinical studies demonstrated a favourable effect by nimodipine on the severity of neurological deficits caused by cerebral vasospasm following SAH, there is no arteriographic evidence that the drug either prevents or relieves the spasm of these arteries. The actual mechanism of action in humans is, therefore, unknown.

Pharmacokinetic Properties

Absorption

The orally administered active substance nimodipine is almost completely absorbed. The unchanged active substance and its early "first pass" metabolites are detected in plasma as little as 10-15 minutes after the ingestion of the tablet. Following multiple-dose oral administration (3 x 30 mg/day), the mean peak plasma concentrations (C_{max}) are 7.3-43.2 ng/mL in elderly individuals, these being reached after 0.6-1.6 h (t_{max}). The peak plasma concentration and the area under the curve increase proportionally to the dose up to the highest dose under test (90 mg).

Using continuous infusions of 0.03 mg/kg/h, mean steady-state plasma concentrations of 17.6-26.6 ng/mL are achieved. After intravenous bolus injections, the plasma nimodipine concentrations fall biphasically with half-lives of 5-10 minutes and about 60 minutes. The distribution volume (V_{ss} , 2-compartment model) for intravenous 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.



Mean plasma nimodipine concentration curves after oral administration of 30 mg in tablet form, and following intravenous infusion of 0.015 mg/kg for 1 hour. (n = 24 volunteers).

Nimodipine undergoes extensive first pass metabolism in the liver. The mean bioavailability of nimodipine tablets ranges from \pm 3-12% in healthy individuals to 16% (range 3-30%) in patients with SAH.

Bioavailability is significantly increased in patients with hepatic disease (e.g., cirrhosis) with C_{max} approximately double that in normal patients which necessitates lowering the dose in this group of patients (see DOSAGE AND ADMINISTRATION).

The effects of a standard breakfast on the bioavailability of nimodipine tablets were investigated in two separate studies. From the results it was concluded that, although the rate of absorption is delayed as evidenced by the decrease in C_{max} (of approx. 40%) and the increase of t_{max} (approx. 100%), the presence of food does not alter the extent of absorption of nimodipine tablets.

Distribution

Studies in animals indicate that nimodipine is widely distributed into body tissues after oral or intravenous administration. Following intravenous administration in healthy individuals, nimodipine distributes rapidly into the central compartment with a half-life of approximately 6-7 minutes; the volume of distribution of the central compartment averaged 0.43 L/kg. The steady-state volume of distribution following intravenous administration has been reported to range from 0.94-2.3 L/kg. Plasma protein binding of unchanged nimodipine averages more than 95% and is independent of concentration over a range of 10 ng/mL to 10 μ g/mL.

Nimodipine appears to distribute to a limited extent into CSF. During intravenous infusion of nimodipine at a rate of 2 mg/hour for up to 14 days in patients with SAH, mean CSF and plasma concentrations of nimodipine averaged approximately 0.3 and 77 ng/mL, respectively. After oral administration of nimodipine 0.35 mg/kg every 4 hours for 3 weeks, mean CSF and plasma nimodipine concentrations were 0.77 and 6.9 ng/mL, respectively. However, concentrations as high as 12.5 ng/mL reportedly have been detected.

Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. Nimodipine itself has been shown to appear in human breast milk; the concentrations were lower than in maternal plasma.

Elimination

Nimodipine concentrations appear to decline in a biphasic manner. The half-life ($T_{1/2}$) was 1.2-1.8 hours after intravenous infusion; after oral administration, the elimination $T_{1/2}$ was 5-10 hours and dose-independent. The elimination $T_{1/2}$ from plasma of total radioactivity was 14 hours with ^3H nimodipine.

No sign of accumulation was noted in patients receiving 40 mg nimodipine three times daily for 7 days.

Nimodipine is extensively metabolised in the liver via the cytochrome P450 3A4 system, with approximately 10%, or less than 1%, of an orally administered dose present in plasma or urine, respectively, as unchanged drug (see Interactions with other Medicines). All metabolites of nimodipine are either inactive or substantially less active than the parent drug.

Cumulative excretion of metabolites in urine is approximately 50% of the dose after 48 hours and 30% in faeces.

Plasma clearance of nimodipine varies considerably, averaging 0.84 L/kg per hour (range: 0.51-1.15 L/kg per hour) in healthy individuals and 1.18 L/kg per hour (range: 0.57-1.77 L/kg per hour) in patients with SAH. Clearance of nimodipine may be decreased substantially in patients with hepatic dysfunction.

Patients with renal impairment showed a substantial prolongation of nimodipine elimination half-life and a reduction in plasma clearance of the drug compared with healthy individuals. These findings may have been attributable in part to age related reductions in liver function in patients with renal impairment, who were substantially older (mean age 65.3 years) than healthy controls (mean age 25.2 years). An additional study in patients with different degrees of creatinine clearance suggests no systemic accumulation of the drug.

INDICATIONS

Prophylaxis and treatment of ischaemic neurological deficits caused by cerebral vasospasm after subarachnoid haemorrhage following ruptured intracranial aneurysm, in patients who are in good neurological condition post-ictus, e.g., Hunt and Hess Grades I-III (see PHARMACOLOGY).

CONTRAINDICATIONS

NIMOTOP TABLETS AND CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Hypersensitivity to nimodipine or any of the excipients.

NIMOTOP TABLETS

The use of nimodipine in combination with rifampicin is contraindicated as efficacy of Nimotop tablets may be significantly reduced when concomitantly administered with rifampicin (see Interactions with other medicines).

The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin or carbamazepine is contraindicated as efficacy of nimodipine tablets may be significantly reduced (see Interactions with other medicines).

PRECAUTIONS

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION AND NIMOTOP TABLETS

Blood Pressure

Nimodipine has the haemodynamic effects expected of a calcium channel blocker although they are generally not marked at usual therapeutic doses. Blood pressure should be carefully monitored during treatment with nimodipine as a decrease in blood pressure has been reported in about 5% to 7% of SAH patients receiving oral nimodipine. Caution is required in patients with hypotension (systolic pressure lower than 100 mm Hg). The use of nimodipine is not generally recommended in patients taking antihypertensive drugs, including other calcium channel blockers, since it may potentiate the effects of these medications.

Simultaneous intravenous administration of β -blockers can lead to the mutual potentiation of negative inotropic effects and even to decompensated heart failure.

Please refer also to the section on Renal Dysfunction.

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 ischaemia) versus the benefit (e.g. improvement of brain perfusion).

Cerebral Oedema or Severely Raised Intracranial Pressure

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

Renal Dysfunction

There are insufficient data on patients with impaired renal function. However, patients with severe renal insufficiency should be carefully monitored with respect to any lowering of blood pressure when receiving nimodipine treatment.

Renal function should be closely monitored during intravenous nimodipine treatment in patients with known renal disease and/or receiving nephrotoxic drugs simultaneously (e.g. aminoglycosides, cephalosporins, frusemide). If deterioration is found discontinuation of the treatment should be considered.

Hepatic Disease

The metabolism of nimodipine is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see DOSAGE AND ADMINISTRATION).

Elevations in one or more liver function test result, including elevated serum concentrations of LDH, alkaline phosphatase, or ALT (SGPT), have been reported in less than 1% of patients with SAH receiving oral nimodipine. Reversible increases in creatinine kinase (CK), creatinine phosphokinase (CPK), AST (SGOT), ALT (SGPT), gamma glutamyl transferase (GGT), gamma-glutamyltranspeptidase (GGTP), bilirubin and amylase also have been reported in patients receiving nimodipine, principally during intravenous administration of the drug. It has been suggested that such increases in liver function test results were caused by alcohol in the intravenous formulation rather than by the drug itself; however, in at least 2 studies, alcohol could not be detected in the blood of patients receiving an alcohol-containing nimodipine injection, and elevated transaminase concentrations also have been reported following oral administration of the drug in clinical studies.

Adverse hepatic effects reported in less than 1% of patients with SAH receiving oral nimodipine include hepatitis and jaundice.

Intestinal Pseudo-obstruction and Ileus

Intestinal pseudo-obstruction (paralytic ileus) has been reported rarely. A causal relationship to nimodipine cannot be ruled out. In three cases, the condition responded to conservative management, but a fourth patient required surgical decompression of the extremely distended colon.

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

When treatment with Nimotop concentrated intravenous infusion solution is administered during pregnancy, the benefits and the potential risks must be carefully assessed according to the severity of the clinical situation.

Nimotop concentrated intravenous infusion solution contains 23.7% ethanol (alcohol), i.e. up to 50 g per daily dose (250mL). 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 product may alter the effects of other medicines (see Interactions with other medicines).

NIMOTOP TABLETS

Nimodipine is metabolised 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 Interactions with other medicines).

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, blood pressure should be monitored and, if necessary, a reduction of the nimodipine dose should be considered.

Dermatologic Effects

Rash, requiring discontinuance of the drug in at least one case, and acne have been reported in less than 1% of patients with SAH receiving oral nimodipine. Pruritus, diaphoresis, and haematoma also have been reported in less than 1% of such patients.

Effects on Fertility

No adverse effects on fertility were observed in male and female rats treated orally with nimodipine at 30 mg/kg/day (0.8 times the maximum recommended human dose on a mg/m² body surface area basis). In single cases of *in vitro* fertilisation calcium channel blockers have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function.

Use in Pregnancy (Category C)

Animal studies have shown no consistent evidence of teratogenic activity in rats or rabbits at oral doses up to 100 mg and 30 mg/kg/day respectively (2.5- and 1.5-times the maximum recommended human dose on a mg/m² body surface area basis), or at intravenous doses up to 0.5 mg/kg/day in both species (estimated relative exposure, 0.1-0.2). Nimodipine was embryotoxic in rats, causing reduced fetal weight from 30 mg/kg/day and resorption at 100 mg/kg/day when administered orally during organogenesis (estimated relative exposure, 0.8 and 2.5, respectively). No embryotoxicity occurred in rabbits at oral doses up to 10 mg/kg/day (estimated relative exposure, 0.5). Peri/postnatal studies in rats showed that oral doses of 30 mg/kg/day were associated with marginally higher incidences of skeletal variation, stunted fetuses and stillbirths. Nimodipine carries the potential to produce fetal hypoxia associated with maternal hypotension.

There are no adequate and well controlled studies in pregnant women to assess directly the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

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

Paediatric Use

Safety and effectiveness in children have not been established.

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.

Genotoxicity

Nimodipine was not mutagenic when tested in bacteria (*S. typhimurium* strains TA98, TA100, TA1535 and TA1537) and yeast (*Saccharomyces cerevisiae*). Weak clastogenicity was observed *in vitro* in assays with Chinese Hamster ovary cells in the presence of metabolic activation, but chromosomal damage was not evident *in vivo* in either the mouse micronucleous test or the dominant lethal test.

Carcinogenicity

Nimodipine was not tumorigenic in male and female mice treated with oral doses up to 546 and 774 mg/kg/day, respectively, for 21 months (estimated relative exposure, 7-10 based on mg/m² body surface area). No treatment-related increase in the incidence of tumours was observed in rats administered oral doses of nimodipine of up to 91 mg/kg/day (males) or 121 mg/kg/day (females) for 2 years (estimated relative exposure, 2-3 based on mg/m² body surface area).

INTERACTIONS WITH OTHER MEDICINES

Hypotensive Agents

In patients with elevated blood pressure who are receiving antihypertensive drugs, Nimotop can potentiate the blood-pressure-lowering effect of the concomitant medication. Blood pressure should be carefully monitored.

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

Rifampicin is expected to increase the rate of metabolism of Nimotop tablets due to enzyme induction, as experienced with other calcium antagonists such as nifedipine. Thus, the efficacy of Nimotop tablets may be significantly reduced when concomitantly administered with rifampicin. The use of nimodipine in combination with rifampicin is therefore contraindicated (see CONTRAINDICATIONS).

Anticonvulsants

Few data are available on the interaction of nimodipine and anticonvulsant drugs. However, a study of epileptic patients receiving long-term treatment with the anticonvulsants carbamazepine, phenobarbitone or phenytoin, either alone or in combination, showed that plasma concentrations of nimodipine given as a single oral dose of 60 mg were markedly reduced (approx. 7 fold decrease in AUC and 8-10 fold in C_{max}). This was due to the well-known enzyme inducing properties of these antiepileptic drugs, leading to a reduced oral bioavailability of nimodipine by

enhanced first pass metabolism. This phenomenon has been reported for many high clearance drugs like nimodipine and also for other dihydropyridine calcium antagonists.

Thus, the concomitant administration of anticonvulsants and oral nimodipine is contraindicated in epileptic patients or patients on long-term/chronic anticonvulsant therapy, because the nimodipine serum concentration may be considerably lowered due to the induction of drug-metabolising enzymes (see CONTRAINDICATIONS).

A general guide concerning dose adjustments of nimodipine tablets is not possible because the extent of enzyme induction and changed capacity for nimodipine first pass metabolism may show large inter-individual differences.

Conversely, nimodipine plasma concentrations following administration of 60 mg single oral dose were increased (approx. 50%) in epileptic patients on long-term sodium valproate therapy. These patients may require smaller doses. The simultaneous administration of valproic acid can lead to an increase in the plasma nimodipine concentration (see PRECAUTIONS).

Effect of Nimodipine on Anticonvulsant therapy:

No effect was observed on the steady state plasma concentrations of the abovementioned anticonvulsants following the administration of a single oral 60 mg dose of nimodipine. Multiple dosing has not been investigated, but no effect of nimodipine on the bioavailability of these drugs is expected.

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 DOSAGE AND 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 PRECAUTIONS). Azithromycin, although structurally related to the class of macrolide antibiotic, does not inhibit CYP3A4.

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 PRECAUTIONS).

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 PRECAUTIONS).

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 PRECAUTIONS).

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.

Quinupristin/dalfopristin

Based on experience with the calcium-antagonist nifedipine, co-administration of quinupristin/dalfopristin may lead to increased plasma concentrations of nimodipine (see PRECAUTIONS).

Cimetidine

A study in eight healthy volunteers has shown a 50% increase in mean peak nimodipine plasma concentrations and a 90% increase in the mean area under the curve, after a one-week course of cimetidine at 1,000 mg/day and nimodipine at 90 mg/day. This effect may be mediated by the known inhibition of hepatic cytochrome P-450 by cimetidine, which could decrease first-pass metabolism of nimodipine (see PRECAUTIONS).

Antineoplastic Agents

There is *in vitro* evidence that calcium-channel blocking agents, including nimodipine can enhance the cytotoxic effects of certain antineoplastic agents, e.g., doxorubicin, vincristine, but the clinical importance of these findings remains to be established.

Effects of nimodipine on other drugs

Hypotensive agents

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 zidovudine i.v. and nimodipine bolus i.v. resulted in a significantly higher AUC and significantly reduced distribution volume and clearance for zidovudine.

Other forms of interaction

Because nimodipine concentrated intravenous infusion solution contains 23.7% (v/v) of ethanol, interactions with alcohol-incompatible medicines should be taken into consideration (see PRECAUTIONS).

Renal function can deteriorate if potentially nephrotoxic drugs are given simultaneously with Nimotop IV (see PRECAUTIONS).

Drug-food interaction

Grapefruit juice

Grapefruit juice inhibits the oxidative metabolism of dihydropyridines. Concomitant intake of grapefruit juice and nimodipine can result in increased 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 DOSAGE AND ADMINISTRATION).

ADVERSE EFFECTS

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

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

Uncommon ($\geq 1/1,000$ to $< 1/100$)
 Rare ($\geq 1/10,000$ to $< 1/1,000$)

Table 1. All Adverse Drug Reactions reported in patients in multiple clinical trials in MedDRA Coding.

System Organ Class (MedDRA)	Uncommon	Rare
Blood and the lymphatic system disorders	Thrombocytopaenia	
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
General disorders and administrative site conditions		Injection and infusion site reactions Infusion site (thrombo-)phlebitis*

* "phlebitis" coded by COSTART terminology, occurred at a frequency of 0.6% (uncommon) in placebo-controlled trials.

Post Marketing Adverse Events

Events described in MedDRA preferred terms:

Investigations/ Vascular disorders: hypotension

Nervous system disorders: headache

Gastrointestinal: nausea and vomiting

DOSAGE AND ADMINISTRATION

Dosage: NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

For single use in one patient only. Discard any residue.

Continuous intravenous infusion:

Nimotop concentrated intravenous infusion solution must be administered by co-infusion via a three-way stopcock to the central catheter. The initial dosage is 5 mL Nimotop concentrated intravenous solution (= 1 mg nimodipine) per hour infused continuously for the first 2 hours (approximately 15 µg/kg body weight/hr). Co-infusion solution must be administered at a rate of 20 mL per hour with this initial dosage. If this dosage is tolerated, particularly if there is no severe reduction in blood pressure, the dosage should then be increased to 10 mL Nimotop concentrated intravenous infusion solution per hour (= 2 mg nimodipine/h) (approximately 30 µg/kg body weight/hr) with a corresponding increase in the rate of co-infusion solution to 40 mL per hour.

Patients whose body weights are distinctly below 70 kg or who have labile blood pressure can start with a dose of 2.5 mL Nimotop concentrated intravenous infusion solution/hr (= 0.5 mg nimodipine/h) with corresponding reduction in the rate of co-

infusion and, if at all possible, the dosage should not be raised above 5 mL nimodipine concentrated intravenous infusion solution per hour. The treatment should be discontinued if necessary.

Intracisternal Instillation:

Intracisternal instillation has been employed in uncontrolled trials in combination with IV/oral administration. A 1: 19 ratio for dilution with Ringer's was tested *in vitro* with a very small risk of crystallisation. The dilute solution of nimodipine was used immediately after preparation. If the dilute solution is not used immediately, it should be discarded.

Patients with hepatic insufficiency may have substantially reduced clearance and approximately doubled plasma concentration; dosage should be reduced to 2.5 mL Nimotop concentrated intravenous infusion solution per hour and/or one Nimotop tablet (30 mg) every 4 hours in these patients.

In cases of severely disturbed kidney or liver function, particularly in cirrhosis of the liver, the effects and side effects, e.g., the reduction in blood pressure, may be more pronounced. In such cases the dose should, if necessary, be reduced in accordance with blood pressure monitoring and the ECG.

Dosage: NIMOTOP TABLETS

Prophylaxis and Treatment: Following parenteral administration of Nimotop concentrated intravenous infusion solution for 5-14 days, a dose of 2 Nimotop tablets (2 x 30 mg) 6 times a day at 4 hourly intervals (6 x 30 mg nimodipine/day) is recommended for about 7 days. Where only oral treatment is considered, the recommended dosage is 2 Nimotop tablets (2 x 30 mg) 6 times a day for 10-14 days.

Patients with hepatic insufficiency may have substantially reduced clearance and approximately doubled maximum plasma concentration; accordingly, the dosage should be reduced to one Nimotop tablet (30 mg) every 4 hours in these patients. If necessary, discontinuation of Nimotop should be considered.

Due to the possibility of hydrolysis in high alkaline pH, alkaline mixtures should not be given for 2 hours before or after administering Nimotop tablets.

Drug effects should be carefully monitored in all patients, particularly if higher doses are used. Upon co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers a dose-adaptation may be necessary (see Interactions with other medicines).

Administration: NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Nimotop concentrated intravenous infusion solution is administered as a continuous intravenous infusion via a central catheter using an infusion pump. A three-way stopcock should be used to connect the Nimotop polyethylene tube with the co-infusion line and the central catheter.

Only infusion pumps with polyethylene (PE) infusion tubing, polypropylene (PP) syringes and polyethylene or polypropylene extensions, taps, connectors may be used. Do not use polyvinylchloride (PVC) infusion tubing as nimodipine is adsorbed by the tubing.

Polyethylene or polyurethane catheters are to be used, only in conjunction with a polycarbonate stop-cock.

PVC Y-connector tubing must not be used and the rates of administration of recommended co-infusion solutions must be followed due to the possibility of crystal formation as seen in *in vitro* tests with Nimotop concentrated intravenous infusion solution at higher dilutions.

All infusion tubings must be changed every 24 hours.

Nimotop concentrated intravenous infusion solution should be co-infused with approximately 40 mL/h of any of the following infusion solutions which are compatible at the recommended 1 to 4 mixing ratio:

Sodium chloride intravenous infusion 0.9%, glucose intravenous infusion 5% (Glucose 5%), compound sodium lactate intravenous infusion solution (Hartmann's solution for injection/lactated Ringer's solution), lactated Ringer's solution with magnesium, Dextran 40, Mannitol (10%), hetastarch 6% (Poly (0-2-hydroxyethyl) starch 6%), Human albumin 5% or blood.

Nimotop concentrated intravenous infusion solution must not be mixed with any other drugs and must not be added to an infusion bag or bottle. Infusion solutions other than those recommended above should not be used. Nimotop concentrated intravenous infusion solution has a pH of 6.8.

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

Nimodipine concentrated intravenous infusion solution is slightly light-sensitive. Its use in direct sunlight should be avoided. No special protective measures need be taken for up to 10 hours if Nimotop concentrated intravenous infusion solution is being administered in diffuse daylight or in artificial light.

Administration of Nimotop concentrated intravenous infusion solution and Nimotop tablets (30 mg) should be continued during anaesthesia, surgery, and angiography.

Administration: NIMOTOP TABLETS

The tablets should be swallowed whole with liquid, irrespective of meal times. Grapefruit juice is to be avoided (see Interactions with other medicines).

Duration of Administration

Prophylaxis and treatment of ischaemic symptoms caused by vasospasm after subarachnoid haemorrhage should commence as soon as possible or within 4 days of the diagnosis of SAH and continue for at least 7 days up to a maximum of 14 days.

If during prophylactic administration of nimodipine, the source of the haemorrhage is treated surgically, intravenous treatment with nimodipine 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 (see Dosage: NIMOTOP TABLETS).

OVERDOSAGE

Symptoms of Overdosage

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

Treatment of Overdosage

In the event of acute overdosage, treatment with Nimotop must be discontinued immediately. Active cardiovascular support should include close monitoring of cardiac and respiratory function. Intravenous dopamine or noradrenaline may be helpful in restoring blood pressure. Since no specific antidote is known, subsequent treatment for other side effects should be governed by the most prominent symptoms. Since Nimotop is highly protein bound, dialysis is not likely to be of benefit.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Clear slightly yellowish solution containing 10 mg nimodipine/50 mL and 10 g alcohol/ 50 mL. Packs of 5 vials.

Nimotop concentrated intravenous infusion solution has good stability, but is somewhat sensitive to light, and therefore must not be used in direct sunlight. The product should be stored in the manufacturer's light-protective glass bottle container within the cardboard carton. If appropriate, infusion pumps and tubing must be protected with opaque coverings, or black, brown, yellow or red infusion lines can be used. However, in diffuse daylight or artificial light, Nimotop concentrated intravenous infusion solution can be used for up to 10 hours without protection from light. Protect from freezing. Store below 25°C.

NIMOTOP TABLETS

Round convex, yellow film-coated tablets containing 30 mg nimodipine marked "SK" on top and the Bayer cross on the bottom. Packs of 100 tablets.

Tablets are packed in foil blisters of polypropylene/aluminium (store below 25°C).

Nimotop tablets should be stored in the manufacturer's original container in a dry place and protected from direct light.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
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875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

9 June 1993

DATE OF MOST RECENT AMENDMENT

18 April 2017

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