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2/08

NIMOTOP®
(nimodipine)
CAPSULES
For Oral Use

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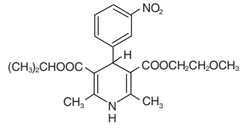
DO NOT ADMINISTER NIMOTOP INTRAVENOUSLY OR BY OTHER PARENTERAL ROUTES. DEATHS AND SERIOUS, LIFE THREATENING ADVERSE EVENTS HAVE OCCURRED WHEN THE CONTENTS OF NIMOTOP CAPSULES HAVE BEEN INJECTED PARENTERALLY (See WARNINGS and DOSAGE AND ADMINISTRATION).

DESCRIPTION

Nimotop® (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 - (m-nitrophenyl) - 3, 5 - pyridinedicarboxylate. It has a molecular weight of 418.5 and a molecular formula of $C_{21}H_{26}N_2O_7$. The structural formula is:



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

NIMOTOP® capsules are formulated as soft gelatin capsules for oral administration. Each liquid filled capsule contains 30 mg of nimodipine in a vehicle of glycerin, peppermint oil, purified water and polyethylene glycol 400. The soft gelatin capsule shell contains gelatin, glycerin, purified water and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Nimodipine is a calcium channel blocker. The contractile processes of smooth muscle cells are dependent upon calcium ions, which enter these cells during depolarization as slow ionic transmembrane currents. Nimodipine inhibits calcium ion transfer into these cells and thus inhibits contractions of vascular smooth muscle. In animal experiments, nimodipine had a greater effect on cerebral arteries than on arteries elsewhere in the body perhaps because 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 hemorrhage (SAH) patients.

The precise mechanism of action of nimodipine in humans is unknown. Although the clinical studies described below demonstrate a favorable effect of 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. However, whether or not the arteriographic methodology utilized was adequate to detect a clinically meaningful effect, if any, on vasospasm is unknown.

Pharmacokinetics and Metabolism: In man, nimodipine is rapidly absorbed after oral administration, and peak concentrations are generally attained within one hour. The terminal elimination half-life is approximately 8 to 9 hours but earlier elimination rates are much more rapid, equivalent to a half-life of 1–2 hours; a consequence is the need for frequent (every 4 hours) dosing. There were no signs of accumulation when nimodipine was given three times a day for seven days. Nimodipine is over 95% bound to plasma proteins. The binding was concentration independent over the range of 10 ng/mL to 10 µg/mL. Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. Numerous metabolites, all of which are either inactive or considerably less active than the parent compound, have been identified. Because of a high first-pass metabolism, the bioavailability of nimodipine averages 13% after oral administration. The bioavailability is significantly increased in patients with hepatic cirrhosis, with C_{max} approximately double that in normals which necessitates lowering the dose in this group of patients (see **DOSAGE AND ADMINISTRATION**). In a study of 24 healthy male volunteers, administration of nimodipine capsules following a standard breakfast resulted in a 68% lower peak plasma concentration and 38% lower bioavailability relative to dosing under fasted conditions.

In a single parallel-group study involving 24 elderly subjects (aged 59–79) and 24 younger subjects (aged 22–40), the observed AUC and C_{max} of nimodipine was approximately 2-fold higher in the elderly population compared to the younger study subjects following oral administration (given as a single dose of 30 mg and dosed to steady-state with 30 mg t.i.d. for 6 days). The clinical response to these age-related pharmacokinetic differences, however, was not considered significant. (See **PRECAUTIONS: Geriatric Use.)**

Clinical Trials: Nimodipine has been shown, in 4 randomized, double-blind, placebo-controlled trials, to reduce the severity of neurological deficits resulting from vasospasm in patients who have had a recent subarachnoid hemorrhage (SAH). The trials used doses ranging from 20–30 mg to 90 mg every 4 hours, with drug given for 21 days in 3 studies, and for at least 18 days in the other. Three of the four trials followed patients for 3–6 months. Three of the trials studied relatively well patients, with all or most patients in Hunt and Hess Grades I – III (essentially free of focal deficits after the initial bleed) the fourth studied much sicker patients, Hunt and Hess Grades III – V. Two studies, one U.S., one French, were similar in design, with relatively unimpaired SAH patients randomized to nimodipine or placebo. In each, a judgment was made as to whether any late-developing deficit was due to spasm or other causes, and the deficits were graded. Both studies showed significantly fewer severe deficits due to spasm in the nimodipine group; the second (French) study showed fewer spasm-related deficits of all severities. No effect was seen on deficits not related to spasm.

				Patients		
Study	**Dose**	**Grade***		**Number Analyzed**	**Any Deficit Due to Spasm**	**Numbers with Severe Deficit**
U.S.	20-30 mg	I-III	Nimodipine Placebo	56 60	13 16	1 8**
French	60 mg	I-III	Nimodipine Placebo	31 39	4 11	2 10**

* Hunt and Hess Grade

** p=0.03

A third, large, study was performed in the United Kingdom in SAH patients with all grades of severity (but 89% were in Grades I–III). Nimodipine was dosed 60mg every 4 hours. Outcomes were not defined as spasm related or not but there was a significant reduction in the overall rate of infarction and severely disabling neurological outcome at 3 months:

	Nimodipine	**Placebo**
Total patients	278	276
Good recovery	199*	169
Moderate disability	24	16
Severe disability	12**	31
Death	43***	60

* p = 0.0444 - good and moderate vs severe and dead

** p = 0.001 - severe disability

*** p = 0.056 - death

A Canadian study entered much sicker patients, (Hunt and Hess Grades III-V), who had a high rate of death and disability, and used a dose of 90 mg every 4 hours, but was otherwise similar to the first two studies. Analysis of delayed ischemic deficits, many of which result from spasm, showed a significant reduction in spasm-related deficits. Among analyzed patients (72 nimodipine, 82 placebo), there were the following outcomes.

	Delayed Ischemic Deficits (DID)		**Permanent Deficits**	
	Nimodipine n (%)	**Placebo n (%)**	**Nimodipine n (%)**	**Placebo n (%)**
DID Spasm Alone	8 (11)*	25 (31)	5 (7)*	22 (27)
DID Spasm Contributing	18 (25)	21 (26)	16 (22)	17 (21)
DID Without Spasm	7 (10)	8 (10)	6 (8)	7 (9)
No DID	39 (54)	28 (34)	45 (63)	36 (44)

* p = 0.001, nimodipine vs placebo

When data were combined for the Canadian and the United Kingdom studies, the treatment difference on success rate (i.e. good recovery) on the Glasgow Outcome Scale was 25.3% (nimodipine) versus 10.9% (placebo) for Hunt and Hess Grades IV or V . The table below demonstrates that nimodipine tends to improve good recovery of SAH patients with poor neurological status post-ictus, while decreasing the numbers with severe disability and vegetative survival.

Glasgow Outcome*	Nimodipine (n=87)	Placebo (n=101)
Good Recovery	22 (25.3%)	11 (10.9%)
Moderate Disability	8 (9.2%)	12 (11.9%)
Severe Disability	6 (6.9%)	15 (14.9%)
Vegetative Survival	4 (4.6%)	9 (8.9%)
Death	47 (54.0%)	54 (53.5%)

* p = 0.045, nimodipine vs placebo

A dose-ranging study comparing 30, 60 and 90 mg doses found a generally low rate of spasm-related neurological deficits but no dose response relationship.

INDICATIONS AND USAGE

Nimotop® (nimodipine) is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V).

CONTRAINDICATIONS

Nimotop capsules must not be used in patients with hypersensitivity to nimodipine or to any of the excipients.

The use of nimodipine in combination with rifampin is contraindicated as efficacy of nimodipine capsules could be significantly reduced when concomitantly administered with rifampin. (See **PRECAUTIONS**, Drug Interactions).

The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin or carbamazepine is contraindicated as efficacy of nimodipine capsules could be significantly reduced. (See **PRECAUTIONS**, Drug Interactions).

WARNINGS

DEATH DUE TO INADVERTENT INTRAVENOUS ADMINISTRATION:

DO NOT ADMINISTER NIMOTOP INTRAVENOUSLY OR BY OTHER PARENTERAL ROUTES. DEATHS AND SERIOUS, LIFE THREATENING ADVERSE EVENTS, INCLUDING CARDIAC ARREST, CARDIOVASCULAR COLLAPSE, HYPOTENSION, AND BRADYCARDIA, HAVE OCCURRED WHEN THE CONTENTS OF NIMOTOP CAPSULES HAVE BEEN INJECTED PARENTERALLY (SEE DOSAGE AND ADMINISTRATION).

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).

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. However, intravenous administration of the contents of Nimotop Capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension, and bradycardia. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers. (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**)

Hepatic Disease: The metabolism of Nimotop® 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**).

Intestinal pseudo-obstruction and ileus have been reported rarely in patients treated with nimodipine. A causal relationship has not been established. The condition has responded to conservative management.

Laboratory Test Interactions: None known.

Drug Interactions: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension; this phenomenon was not observed in North American clinical trials.

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.

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.

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

Rifampin
From the experience with other calcium antagonists it has to be expected that rifampin accelerates the metabolism of nimodipine due to enzyme induction. Thus, efficacy of nimodipine could be significantly reduced when concomitantly administered with rifampin. The use of nimodipine in combination with rifampin 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 adjustment 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, Drug Interactions**).

Azithromycin, although structurally related to the class of macrolide antibiotics 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.

A study in eight healthy volunteers has shown a 50% increase in mean peak nimodipine plasma concentrations and a 90% increase in 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.

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 administered 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 the anti-HIV drug zidovudine i.v. and nimodipine bolus i.v. resulted in significantly higher AUC of zidovudine, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant, however, and the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenicity studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral doses of 1 and 10 mg/kg/day administered (by gavage) from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. 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/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. 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.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Clinical studies of nimodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosing in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

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.

ADVERSE REACTIONS
Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					
Sign/Symptom	**0.35 mg/kg (n=82)**	**30 mg (n=71)**	**60 mg (n=494)**	**90 mg (n=172)**	**120 mg (n=4)**	**Placebo (n=479)**
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia; anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were: itching, gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting; diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

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No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

DRUG ABUSE AND DEPENDENCE
There have been no reported instances of drug abuse or dependence with Nimotop®.

OVERDOSAGE
There have been no reports of overdosage from the oral administration of Nimotop®.

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 nimodipine 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.

Since Nimotop® is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION
DO NOT ADMINISTER NIMOTOP CAPSULES INTRAVENOUSLY OR BY OTHER PARENTERAL ROUTES (see WARNINGS). If Nimotop is inadvertently administered intravenously, clinically significant hypotension may require cardiovascular support with pressor agents. Specific treatments for calcium channel blocker overdose should also be given promptly.

Nimotop is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

Unless otherwise prescribed, the oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. In general, the capsules should be swallowed whole with a little liquid, preferably not less than one hour before or two hours after meals. Grapefruit juice is to be avoided (See **PRECAUTIONS**, Drug Interactions). Oral Nimotop® therapy should commence as soon as possible or within 96 hours of the diagnosis of subarachnoid hemorrhage (aSAH).

Duration of use:
Nimodipine capsules may be used during anaesthesia or surgical procedures. In the event of surgical invention, administration of nimodipine should be continued, with dosages as above, to complete the 21 day period.

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. A parenteral syringe can be used to extract the liquid inside the capsule, but the liquid should always be transferred to a syringe that cannot accept a needle and that is designed for administration orally or via a naso-gastric tube or PEG. To help minimize administration errors, it is recommended that the syringe used for administration be labeled "Not for IV Use". The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%). The efficacy and safety of this method of administration has not been demonstrated in clinical trials.

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

Severely disturbed liver function, particularly liver cirrhosis, may result in an increased bioavailability of nimodipine due to a decreased first pass capacity and a reduced metabolic clearance. The effects and side-effects, e.g. reduction in blood pressure, may be more pronounced in these patients. Dosage should be reduced to one 30 mg capsule every 4 hours with close monitoring of blood pressure and heart rate; if necessary, discontinuation of the treatment should be considered.

Upon co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers a dose adjustment may be necessary.

HOW SUPPLIED
Each ivory colored, soft gelatin NIMOTOP® capsule is imprinted with the word Nimotop and contains 30 mg of nimodipine. The 30 mg capsules are packaged in unit dose foil pouches and supplied in cartons containing 100 capsules. The product is also available in child resistant unit dose safety pak foil pouches containing 30 capsules per carton. The capsules should be stored in the manufacturer's original foil package at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [See USP controlled Room Temperature.]

Capsules should be protected from light and freezing.

	Strength	**NDC Code**	**Capsule Identification**
Unit Dose Package of 100:	30 mg	50419-855-48	Nimotop
Unit Dose Package of 30:	30 mg	50419-855-70	Nimotop

Bayer HealthCare Pharmaceuticals

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