

PRODUCT MONOGRAPH

**Pr****NIMOTOP<sup>®</sup> Tablets**

nimodipine tablets Bayer Standard

30 mg

Adjunct in the Management of  
Subarachnoid Hemorrhage

Calcium Channel Blocking Agent

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## PrNIMOTOP® Tablets

nimodipine tablets Bayer Standard

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

**Table 1 – Product Information Summary**

<b>Route of Administration</b>	<b>Dosage Form, Strength</b>	<b>Nonmedicinal Ingredients</b>
oral	tablets, 30 mg	Crospovidone, ferric oxide yellow, hypromellose, macrogol, magnesium stearate, maize starch, microcrystalline cellulose, povidone, and titanium dioxide

#### INDICATIONS AND CLINICAL USE

##### Adults

NIMOTOP Tablets (nimodipine tablets) may be useful as an adjunct to improve the neurologic outcome following subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysm.

##### Geriatrics (> 65 years of age)

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 elderly and younger patients. In general, dosing for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

##### Pediatrics (< 18 years of age)

The safety and effectiveness of nimodipine in children have not been established.

#### CONTRAINDICATIONS

- Hypersensitivity to nimodipine or to any ingredient of the drug product.
- The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin, or carbamazepine is contraindicated, as the efficacy of nimodipine tablets could be significantly reduced.
- The use of nimodipine in combination with rifampin is contraindicated, as the efficacy of nimodipine tablets could be significantly reduced when concomitantly administered with rifampin.

## **WARNINGS AND PRECAUTIONS**

### **General**

NIMOTOP Tablets (nimodipine tablets) should only be used with great caution when cerebral edema or severely raised intracranial pressure is present. 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).

NIMOTOP should not be used in patients with traumatic subarachnoid hemorrhage as a positive benefit to risk ratio has not been established and the specific patient groups that might benefit cannot be identified for this indication.

Caution is required in patients with hypotension (systolic blood pressure lower than 100 mm Hg) (see **WARNINGS AND PRECAUTIONS – Cardiovascular**).

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

NIMOTOP is metabolized via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or induce this enzymatic system may therefore alter the first pass or the clearance of nimodipine. Drugs known to inhibit the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nimodipine are:

- antidepressants (eg, nefazodone and fluoxetine)
- azole antimycotics (eg, ketoconazole)
- cimetidine
- HIV protease inhibitors (eg, ritonavir)
- macrolide antibiotics (eg, erythromycin)
- valproic acid

Upon coadministration with these drugs, blood pressure should be monitored and, if necessary, a reduction of the nimodipine dose should be considered (see **DRUG INTERACTIONS**).

Intestinal pseudo-obstruction (paralytic ileus) has been reported rarely. A causal relationship to NIMOTOP Tablets (nimodipine tablets) 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.

### **Cardiovascular**

NIMOTOP Tablets (nimodipine tablets) have the hemodynamic effects of a calcium channel blocker. In the course of clinical studies in patients with SAH, hypotension was reported in 6.6% of patients with Hunt and Hess grades III to V given 90 mg doses (n = 91), and in 7.5% of patients with grades I and II using 30 to 60 mg doses (n = 255). A fall in blood pressure requiring discontinuation of the drug was reported in 2.2% of the patients in the former group. Hypertensive patients may be more susceptible to a lowering of the blood pressure. Blood pressure should, nevertheless, always be carefully monitored during treatment with nimodipine.

The use of nimodipine is, however, not generally recommended in patients taking antihypertensive drugs, including other calcium channel blockers, since it may potentiate the effects of these medications (see **DRUG INTERACTIONS – Drug-Drug Interactions: Blood Pressure Lowering Drugs**).

Since there has not been a study of NIMOTOP in acute myocardial infarction reported, similar effects of NIMOTOP to that of immediate-release nifedipine cannot be excluded in acute myocardial infarction. Immediate-release nifedipine is contraindicated in acute myocardial infarction.

Some clinical trials have shown that treatment with the immediate-release formulation of the dihydropyridine, nifedipine, in patients with unstable angina, increases the risk of myocardial infarction and recurrent ischemia.

### **Effect on Ability to Drive and Operate Machinery**

Reactions to nimodipine, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery. This is most prevalent at the start of the treatment, upon changing the medication, or in combination with alcohol.

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

### **Hepatic/Biliary/Pancreas**

The metabolism of nimodipine is decreased in patients with impaired hepatic function. Such patients should be given lower doses of the drug and their blood pressure and pulse should be closely monitored.

### **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.

### **Renal**

There are insufficient data on patients with impaired renal function.

### **Special Populations**

#### ***Pregnant Women***

The safety of nimodipine with respect to adverse effects on human fetal development has not been established.

Nimodipine has been shown to have a teratogenic effect in rabbits and to be embryotoxic, causing resorption, stunted growth, and higher incidence of skeletal variations in rats (for details see **TOXICOLOGY - Reproduction Studies**).

Nimodipine should, therefore, not be used during pregnancy unless the potential benefits are considered to justify the potential risk to the fetus (see **TOXICOLOGY – Reproduction Studies**).

**Geriatrics (> 65 years of age)**

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 elderly and younger patients. In general, dosing for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Pediatrics (< 18 years of age)**

The safety and effectiveness of nimodipine in children less than 18 years of age has not been established. Therefore, NIMOTOP is not recommended for use in this patient population.

**ADVERSE REACTIONS**

**Adverse Drug Reaction Overview**

Adverse drug reactions (ADRs) based on placebo-controlled clinical trials with nimodipine have been evaluated in 1395 patients with subarachnoid hemorrhage. In these studies, 703 patients received oral doses of nimodipine and 692 patients received placebo.

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The following are common and less common adverse drug reactions reported by patients in the double-blind, placebo-controlled clinical trial (British Aneurysm and Nimodipine Trial [BRANT Study]):

**Table 2 - Adverse Drug Reactions**

<b>Sign/Symptom</b>	<b>Nimodipine (2 x 30 mg q4h) 60 mg (N = 278) n (%)</b>	<b>Placebo (N = 276) n (%)</b>
<b><i>Blood and Bone Marrow</i></b>		
Anemia	1 (0.4%)	0
Colonic Bleed	1 (0.4%)	0
Hematoma	1 (0.4%)	0
Thrombocytopenia	1 (0.4%)	0
<b><i>Cardiovascular</i></b>		
Headache	3 (1.1%)	1 (0.4%)
Hypertension	1 (0.4%)	0
Hypotension	1 (0.4%)	2 (0.7%)

**Table 2 - Adverse Drug Reactions**

Sign/Symptom	Nimodipine (2 x 30 mg q4h)	Placebo
	60 mg (N = 278) n (%)	(N = 276) n (%)
Vasodilation (Flushing)	1 (0.4%)	0
<b><i>Gastrointestinal Tract</i></b>		
Nausea	1 (0.4%)	0
<b><i>Liver and Biliary System</i></b>		
Jaundice	2 (0.7%)	1 (0.4%)
Liver Function Test Abnormal	2 (0.7%)	4 (1.4%)
<b><i>Respiratory System</i></b>		
Bronchospasm	0	1 (0.4%)
<b><i>Skin</i></b>		
Rash	2 (0.7%)	1 (0.4%)

Abbreviations: N = number of patients; n = number of patients with specific event

Other uncommon or rare adverse drug reactions reported by patients in other SAH clinical trials include allergic reaction, bradycardia, ileus and tachycardia.

**In severely ill patients, there was an overall increased mortality rate in the nimodipine group using the 90 mg q4h dose as compared to placebo.**

Adverse events known to be associated with calcium channel blockers should be appropriately monitored.

### **Postmarket Adverse Drug Reactions**

**Gastrointestinal Disorders:** nausea, vomiting

**Nervous System Disorders:** headache

**Vascular Disorders:** hypotension

### **Abnormal Hematologic and Clinical Chemistry Findings**

Isolated cases of nonfasting 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 INTERACTIONS**

### **Serious Drug Interactions**

- **The concomitant use of oral nimodipine and the antiepileptic drugs phenobarbital, phenytoin, or carbamazepine is contraindicated, as the efficacy of nimodipine tablets could be significantly reduced.**
- **The use of nimodipine in combination with rifampin is contraindicated, as the efficacy of nimodipine tablets could be significantly reduced when concomitantly administered with rifampin.**

## Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via the *CYP3A4* isoenzyme. Coadministration of nimodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered nimodipine to maintain optimum therapeutic blood levels.

Drugs which are known inhibitors of the cytochrome P450 system and therefore may lead to increased plasma concentrations of nimodipine include: azole antifungals, HIV protease inhibitors, fluoxetine, nefazodone, cimetidine, macrolide antibiotics (eg, erythromycin), quinidine and valproic acid. Upon coadministration of nimodipine with these drugs, blood pressure should be monitored and, if necessary, a reduction of the nimodipine dosage should be considered. Consumption of grapefruit juice, a *CYP3A4* inhibitor, prior to or during treatment with nimodipine should be avoided.

The extent as well as the duration of interactions should be taken into account when administering nimodipine together with drugs known to be inducers of the cytochrome P450 system. Concomitant use of nimodipine and phenobarbital, phenytoin, carbamazepine, or rifampin is contraindicated (see **CONTRAINDICATIONS**). Other *CYP3A4* inducers include dexamethasone, rifabutin, and St. John's Wort.

## Drug-Drug Interactions

**Table 3 – Established or Potential Drug-Drug Interactions**

Proper Name	Ref	Effect	Clinical Comment
Alcohol	T	↑ NIMOTOP	Concomitant use of alcohol may potentiate the effect of nimodipine by lowering blood pressure and causing dizziness.
Anticoagulant: warfarin	CT	No effect on NIMOTOP	An interaction study with nimodipine and warfarin has shown no clinically significant interactions between these drugs.
Anticonvulsant: valproic acid	CT	↑ NIMOTOP	In a pharmacokinetic study in epileptic patients receiving long-term treatment concomitant administration of sodium valproate and oral nimodipine resulted in a 50% increase in the bioavailability of nimodipine. Therefore, the simultaneous administration of the anticonvulsant valproic acid can lead to an increase in the plasma nimodipine concentration.
Antidepressant (SSRI): fluoxetine	CT	↑ NIMOTOP	In 39 elderly patients (57-75 years of age) treated with 30 mg nimodipine tid, for at least 3 months, concomitant administration of fluoxetine (20 mg/day for 14 days) resulted in a 50% increase in nimodipine steady-state plasma concentrations. In these patients, fluoxetine plasma concentrations were decreased by approximately 20%, while those of its active metabolite, norfluoxetine, were not significantly affected. In patients receiving fluoxetine, a reduction in nimodipine dosage may be required.
Antidepressant (Tricyclic Antidepressant): nortriptyline	CT	No effect on NIMOTOP	In 12 elderly patients treated with nimodipine (30 mg tid), for at least 3 months, coadministration of nortriptyline (10 mg tid) for 7 days resulted in nonsignificant decreases in nimodipine with AUC <sub>(0-24h)</sub> of 10% and C <sub>max</sub> of 17% at steady state. The pharmacokinetics of nortriptyline were not affected by nimodipine.

**Table 3 – Established or Potential Drug-Drug Interactions**

Proper Name	Ref	Effect	Clinical Comment
Antiepileptic: phenobarbital, phenytoin and/or carbamazepine	CT	↓ NIMOTOP/ ↑ NIMOTOP	A pharmacokinetic study in epileptic patients receiving long-term treatment has shown that concurrent administration of oral nimodipine and <i>CYP450</i> enzyme-inducer antiepileptic drugs (phenobarbital, phenytoin and/or carbamazepine) reduces the bioavailability of nimodipine by about 80%. Concomitant use of nimodipine and phenobarbital, phenytoin, or carbamazepine is contraindicated (see <b>CONTRAINDICATIONS</b> ).
Antipsychotic: haloperidol	CT	No effect on NIMOTOP	In 12 elderly patients (60-80 years of age) receiving haloperidol with an individual but constant dosing (0.7-23.0 mg/day depending on individual need) for at least one month, treatment with 30 mg tid nimodipine for 7 days did not affect the pharmacokinetics of haloperidol.
Anxiolytic, sedative: diazepam	CT	No effect on NIMOTOP	An interaction study with nimodipine and diazepam has shown no clinically significant interactions between these drugs.
Azole Antifungals: ketoconazole	T	↑ NIMOTOP	A formal interaction study investigating the potential drug interaction between nimodipine and ketoconazole has not been performed. Azole antifungals are known to inhibit the <i>CYP3A4</i> 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.
H <sub>2</sub> -receptor antagonist: cimetidine	CT	↑ NIMOTOP	A pharmacokinetic study has shown that concurrent administration of cimetidine and oral nimodipine results in an almost doubling of the area under the nimodipine plasma concentration curve and about a 50% increase in the peak nimodipine plasma concentration. Patients receiving the two drugs concomitantly should be watched carefully for the possible exaggeration of the effects of nimodipine. It may be necessary to adjust the dosage of nimodipine.
HIV Protease Inhibitors: ritonavir	T	↑ NIMOTOP	No formal studies have been performed to investigate the potential interaction between nimodipine and 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 coadministration with these protease inhibitors cannot be excluded.
Macrolide Antibiotics: erythromycin	T	↑ NIMOTOP	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. Therefore, macrolide antibiotics should not be used in combination with nimodipine.

Legend: CT=Clinical Trial; T=Theoretical

### **Blood Pressure Lowering Drugs**

Nimodipine may increase the blood-pressure-lowering effect of concomitantly administered antihypertensives, such as A1-antagonists, ACE inhibitors, alpha-adrenergic blocking agents, methyl dopa, beta-blockers, diuretics, PDE5 inhibitors, and other calcium antagonists. If coadministration with these drugs is unavoidable, careful monitoring of the patient is necessary (see **WARNINGS AND PRECAUTIONS – Cardiovascular**).

In addition to the effect on blood pressure, verapamil and diltiazem are also *CYP3A4* inhibitors and may decrease clearance of nimodipine.

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

### **Drug-Food Interactions**

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  $C_{max}$  (approximately 40%) and the increase in  $T_{max}$  (approximately 100%) the presence of food does not alter the extent of absorption of nimodipine tablets.

Patients should be advised to be consistent in the timing of nimodipine tablet administration, either with or without food.

Published data indicate that through inhibition of cytochrome P450, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. As a consequence, the blood-pressure-lowering effect may be increased. This effect may last for at least 4 days after the last ingestion of grapefruit juice. Therefore, consumption of grapefruit juice prior to or during treatment with nimodipine should be avoided.

### **Drug-Herb Interactions**

Herbal products containing St. John's Wort (*hypericum perforatum*) may lead to a decreased nimodipine plasma concentration. Strong *CYP3A4* inducers should be administered with caution in combination with NIMOTOP Tablets.

## **DOSAGE AND ADMINISTRATION**

### **General Considerations**

NIMOTOP Tablets (nimodipine tablets) contain 30 mg of the active ingredient nimodipine which is consistent with NIMOTOP 30 mg capsules. The 30 mg nimodipine tablet has been shown to provide the same AUC exposure as the 30 mg nimodipine capsule (see **[ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics: Absorption](#)**).

NIMOTOP Tablets should not be dissolved in any type of liquid solution (eg, water, saline) for administration by way of intravenous injection or other parenteral routes.

### **Recommended Dose and Dosage Adjustment**

For the management of neurological deficits following subarachnoid hemorrhage (SAH), NIMOTOP Tablets (nimodipine tablets) therapy should commence as soon as possible or within 4 days of the diagnosis of SAH.

The recommended dosage of NIMOTOP Tablets (nimodipine tablets) is 60 mg (two tablets of 30 mg) administered **orally** every 4 hours for 21 consecutive days after diagnosis of SAH. Doses of up to 90 mg every 4 hours have been used in some patients, although the safety of

higher doses in severely ill patients has not been well established (see **ADVERSE REACTIONS**).

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.

NIMOTOP may be used during anesthesia or surgical procedures. In the event of surgical intervention, administration of NIMOTOP should be continued, with dosages as above, to complete the 21-day period.

Drug effects should be carefully monitored in all patients, particularly if higher doses are used.

### *Special Populations*

#### **Hepatic Impairment**

Patients with hepatic insufficiency may have substantially reduced clearance and approximately doubled maximum plasma concentration; accordingly, the dosage should be reduced to one 30 mg NIMOTOP tablet every 4 hours in these patients.

#### **Renal Impairment**

There are insufficient data on patients with impaired renal function.

#### **Geriatrics (> 65 years of age)**

Clinical studies of nimodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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<sub>max</sub> 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 tid for 6 days). The clinical response to these age-related pharmacokinetic differences, however, was not considered significant.

In general, dosing for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

#### **Pediatrics (< 18 years of age)**

The safety and effectiveness of nimodipine in children less than 18 years of age has not been established. Therefore, NIMOTOP is not recommended for use in this patient population.

### **Missed Dose**

If the patient has forgotten to take a dose, they should be instructed to take it as soon as they remember. The patient should carry on with the remaining days' tablets at the normal four-hour intervals.

A double dose should not be taken to make up for a forgotten tablet.

### **Administration**

The tablets should be swallowed whole with plenty of fluid (preferably a glass of water), independent of meal times. NIMOTOP Tablets should not be crushed as this may result in reduced bioavailability and clinical effectiveness. Tablets should not be taken while lying down. Grapefruit juice is to be avoided. The interval between successive doses should not be less than 4 hours.

### **OVERDOSAGE**

For management of suspected drug overdose, contact your regional Poison Control Centre.
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### **Symptoms of Intoxication**

Symptoms of acute overdose would be related to cardiovascular effects and the patient may experience marked systemic hypotension, tachycardia or bradycardia, flushing, headache, and gastrointestinal complaints and nausea.

### **Treatment of Intoxication**

Clinically significant hypotension due to NIMOTOP overdose may require active cardiovascular support and should include close monitoring of cardiac and respiratory function. In the event of acute overdose, treatment with NIMOTOP must be discontinued immediately. Symptoms of acute overdose are marked lowering of blood pressure, tachycardia or bradycardia, and gastrointestinal complaints and nausea.

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 aimed at the most prominent symptoms. Since nimodipine is 99% bound to serum protein, dialysis is not likely to be of benefit.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Delayed neurological deterioration secondary to cerebral ischemic deficits is believed to be a major determinant of outcome in patients who survive their initial subarachnoid hemorrhage (SAH). NIMOTOP (nimodipine) is a calcium channel blocker of the dihydropyridine group. It

appears to have a more marked effect on the cerebral circulation than on the peripheral circulation. Since it acts on the vascular smooth muscle tone by modifying the contractile process which is dependent upon the movement of extracellular calcium into the cells during depolarization, it was tested in patients with SAH in an effort to improve the neurologic outcome in these patients. Clinical studies with nimodipine support its usefulness as an adjunct in the management of some patients with SAH from ruptured aneurysm by improving their neurologic outcome, particularly in Hunt and Hess grades 1 to 3 patients.

The actual mechanism of the possible beneficial effect of nimodipine is, however, unknown. The original rationale for using nimodipine after SAH was to reduce cerebral arterial spasm, but available evidence indicates that nimodipine does not reduce the incidence or severity of cerebral spasm as seen on angiography.

## **Pharmacokinetics**

### ***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 to 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 to 43.2 ng/mL in elderly individuals, these being reached after 0.6 to 1.6 h ( $T_{max}$ ). Single dosing of 30 mg and 60 mg in young subjects results in mean peak plasma concentrations of  $16 \pm 8$  ng/mL and  $31 \pm 12$  ng/mL, respectively. The peak plasma concentration and the area under the curve increase proportionally to the dose, up to the highest dose under test (90 mg).

A study was conducted to investigate the bioequivalency of NIMOTOP Tablets (nimodipine tablets) and NIMOTOP (Nimodipine Capsules). From the results, it was concluded that the AUCs for the tablet versus the capsules were comparable, 91.1 nanogram hours per millilitre (ng.h/mL) and 103.5 ng.h/mL, respectively, resulting in a ratio of mean AUCs of tablet to capsule of 0.88 (90% two-sided confidence interval (CI): 80% to 97%). The  $C_{max}$  for the tablet was lower than that of the capsule (45.6 ng/mL and 69.1 ng/mL, respectively), with a mean ratio of 0.66 (90% two-sided CI: 55% to 79%). The  $T_{max}$  for the tablet (0.77 h) was longer than that of the capsule (0.59 h). The ratio of the mean  $T_{max}$  for the tablet compared to the capsule was 1.31 with a 90% two-sided CI of 111% to 154%.

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  $C_{max}$  (approximately 40%) and the increase of  $T_{max}$  (approximately 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 administration. Nimodipine is 97% to 99% bound to plasma proteins.

Nimodipine appears to distribute to a limited extent into cerebrospinal fluid (CSF). 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 in the CSF of nimodipine-treated SAH patients.

Nimodipine and/or its metabolites have been shown to appear in rat milk at concentration 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.

### ***Metabolism***

Nimodipine undergoes extensive first pass metabolism in the liver via the cytochrome P450 3A4 system. The mean bioavailability of nimodipine tablets ranges from  $\pm$  3% to 12% in healthy individuals to 16% (range 3% to 30%) in patients with SAH.

Bioavailability is significantly increased in patients with hepatic disease (eg, cirrhosis) with  $C_{max}$  approximately double that in normal patients, which necessitates lowering the dose in this patient population (see **DOSAGE AND ADMINISTRATION - Special Populations: Hepatic Impairment**).

### ***Excretion***

Nimodipine and its metabolites have a dual route of elimination. Approximately 50% of the metabolites undergo renal excretion while 30% are excreted in the feces due to biliary excretion. The metabolites of nimodipine are believed to be either inactive or considerably less active than the parent compound. The elimination kinetics are linear. The half-life for nimodipine is between 1.1 and 1.7 hours and the terminal half-life is approximately 5 to 10 hours and dose-independent.

Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. There were no signs of accumulation in patients receiving 40 mg nimodipine three times daily for seven days.

### **Special Populations and Conditions**

#### ***Geriatrics (> 65 years of age)***

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 were 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 tid for 6 days). The clinical response to these age-related pharmacokinetic differences, however, was not considered significant.

Clinical studies of nimodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dosing for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### ***Pediatrics (< 18 years of age)***

The safety and effectiveness of nimodipine in children have not been established.

### ***Renal Insufficiency***

There are insufficient data on patients with impaired renal function.

### ***Hepatic Insufficiency***

Patients with hepatic insufficiency may have substantially reduced clearance and approximately doubled maximum plasma concentration: accordingly, the dosage should be reduced to one 30 mg NIMOTOP tablet every 4 hours in these patients.

## **STORAGE AND STABILITY**

NIMOTOP tablets should be stored in original packaging between 15 and 30°C. Protect from humidity.

Keep out of reach of children.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

NIMOTOP 30 mg tablets are available in blister packs containing 100 yellow, film-coated, round tablets. Each film-coated tablet is embossed with “BAYER” cross on one side and “SK” on the other side.

Each yellow, film-coated tablet contains 30 mg nimodipine.

### **Nonmedicinal ingredients:**

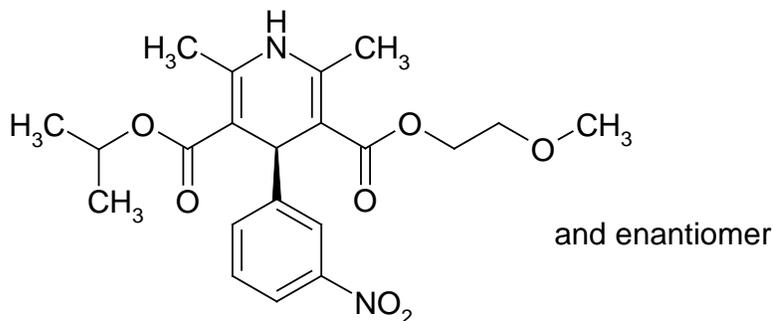
Crospovidone, ferric oxide yellow, hypromellose, macrogol, magnesium stearate, maize starch, microcrystalline cellulose, povidone, and titanium dioxide.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

<b>Proper name:</b>	nimodipine
<b>Chemical name:</b>	isopropyl-(2-methoxyethyl)-1,4-dihydro-2,6-dimethyl-4(3-nitrophenyl)-3,5-pyridinedicarboxylate
<b>Molecular formula:</b>	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O <sub>7</sub>
<b>Molecular mass:</b>	418.4
<b>Structural formula:</b>	



**Physicochemical properties:** Nimodipine is a pyridine dicarboxylic acid dimethylester. It is a finely crystalline yellow substance with a melting point of 125 - 126°C. It is soluble in ethanol, chloroform, ethyl acetate and polyethylene glycol, but insoluble in water.

Nimodipine is stable in neutral and acid media and sensitive to alkalis. It is heat-stable and nonhygroscopic but is moderately sensitive to light, especially in solution.

### CLINICAL TRIALS

The therapeutic usefulness of NIMOTOP Tablets (nimodipine tablets) in patients with SAH was demonstrated in Study 0438 (British Aneurysm and Nimodipine Trial [BRANT Study]). The BRANT Study was a large, randomized, multicentre, placebo-controlled efficacy trial with statistically significantly improved clinical outcome in NIMOTOP patients compared to placebo. The results from this trial were confirmed in a meta-analysis of 12 clinical studies performed up to 2003 using calcium antagonists for aneurysmal SAH. (11-12)

#### BRANT Study Demographics and Trial Design

NIMOTOP Tablets were evaluated at a dose of 2 x 30 mg tablets every 4 hours for 21 days (total dose 360 mg/day) in this placebo-controlled trial. NIMOTOP Tablets were administered to

patients aged 16 to 79 years of age with a clinical diagnosis of SAH confirmed by computed tomography (CT) scan or lumbar puncture and patients were followed-up for three months.

A total of 554 patients were enrolled in this trial, with 278 patients receiving treatment with NIMOTOP Tablets and 276 receiving placebo. All 554 (intent-to-treat) patients were included in the efficacy analysis.

The severity of the SAH was rated according to the five-grade Hunt and Hess scale (5) at study entry. In the BRANT Study, only patients classified neurologically at grades I-III according to the Hunt and Hess scale were included.

Patients with major renal, hepatic, cardiac or pulmonary disease and patients with coma resulting from SAH during the preceding week were excluded from the trial. Patients admitted more than 96 hours after SAH were excluded. (11)

**Table 4: Overview of the BRANT Study Evaluating the Efficacy of NIMOTOP Tablets for SAH**

Study No.:	Trial Design	Dosage, Route of Administration and Duration	Trial Patients (N)	Mean Age (Range) in Years <sup>a</sup>	Gender <sup>a</sup>
0438 (11)	Randomized, double-blind, placebo-controlled, multicentre trial (BRANT Study - United Kingdom)	2 x 30 mg tablets every 4 hours, oral, for 21 days with 3 month follow-up	NIMOTOP N = 278 (Hunt and Hess Grades I-III) Placebo: N = 276	47 (20 - 79)	M = 221 F = 333

Abbreviations: F = Female, M = Male, mg = milligram, N = Patients Valid for Intent-to-Treat Analysis

a Based on patients valid for efficacy analysis

### **Efficacy of NIMOTOP Tablets in Patients with SAH**

Primary efficacy endpoints in the BRANT Study included assessment of overall clinical outcome of patients as classified by the 5-point Glasgow Outcome Scale (death, persistent vegetative state, severe disability, moderate disability, and good recovery) and mortality. For overall outcome, the Glasgow Outcome Scale was separated into two categories of good outcome (good recovery and moderate disability) versus poor outcome (severe disability and persistent vegetative state and death). Ischemic neurological deficit and the incidence of cerebral infarct were also evaluated in the BRANT Study.

### **Study Results**

A summary of the overall clinical outcome of patients in the BRANT placebo-controlled study is provided in Table 5:

**Table 5: Overall Clinical Outcome of Patients with SAH in the Placebo-Controlled BRANT Study**

Clinical Study	Nimodipine			Placebo		Total (N)
	Good <sup>a</sup> N (%)	Poor <sup>b</sup> N (%)	Total (N)	Good <sup>a</sup> N (%)	Poor <sup>b</sup> N (%)	
0438	223 (80.2)	55 (19.8)	278	185 (67.0)	91 (33.0)	276

Abbreviations: N = number of patients, SAH = subarachnoid hemorrhage

a Good outcome = good recovery and moderate disability

b Poor outcome = severe disability, persistent vegetative state, death

A clear benefit from NIMOTOP treatment was demonstrated in all 3 primary endpoints in this study. The incidence of cerebral infarct was 22% (61/278) in the NIMOTOP group compared to 33% (92/276) in the placebo group; a reduction of 34% ( $P < 0.01$ ). A significantly improved clinical outcome at 3 months was observed, with 80% (223/278) of NIMOTOP patients having a good recovery or moderate disability compared with 67% (185/276) of placebo patients ( $P < 0.0005$ ). Correspondingly there was a 40% reduction in patients with a poor outcome in the NIMOTOP group with 20% (55/278) versus 33% (91/276) in the placebo group.

No significant difference in mortality was observed in the BRANT Study. There were 103 deaths (18.6%) with 43 (15.5%) in the NIMOTOP group and 60 (21.7%) in the placebo group.

### **Cochrane Collaboration®**

A meta-analysis and review of 12 randomized, controlled clinical studies was conducted with calcium antagonists in aneurysmal SAH. (12) A total of 2844 randomized male and female patients aged 44 to 56 years (1396 in the treatment group and 1448 in the control group) were included in the analysis. The drugs investigated included nimodipine in 8 studies (1574 patients), nicardipine in 2 studies (954 patients), AT877 (Fasudil Hydrochloride) in 1 study (276 patients), and magnesium in 1 study (40 patients). The results of this analysis confirmed that NIMOTOP reduces the risk of poor outcome (defined as death, vegetative state, or severe disability) and secondary ischemia in aneurysmal SAH.

### **Clinical Conclusions**

The results of the BRANT Study support the efficacy and therapeutic usefulness of NIMOTOP Tablets in patients with SAH specifically for the improvement of neurological outcome caused by a ruptured intracranial aneurysm. The clinical outcome, as classified by the Glasgow Outcome Scale, was separated into two categories, good outcome versus poor outcome. A statistically significant improvement in clinical outcome was observed with NIMOTOP. Poor outcomes were reduced by 40% with 80% of NIMOTOP patients assessed as having a good outcome (good recovery and moderate disability), versus 67% of placebo patients. The incidence of cerebral infarction was reduced by 34% (22% in the nimodipine group versus 33% in the placebo group).

## **DETAILED PHARMACOLOGY**

### **Animal Pharmacology**

Nimodipine dilates the cerebral vessels and increases cerebral blood flow after intra-arterial (internal carotid artery), intravenous, oral, and sublingual administration in several animal species investigated (mouse, rat, rabbit, cat, dog, rhesus and squirrel monkeys). It dilates not only the smaller cerebral vessels, but also larger cerebral arteries such as the basilar artery. The increase in cerebral blood flow is dose-dependent, achieving in the highest dosage a 70% to 100% increase in comparison to the premedication value. The effective dose range is 0.001 to 0.1 mg/kg IV. and 0.01 to 2.0 mg/kg orally.

Nimodipine is highly lipophilic, allowing it to cross the blood-brain barrier. This was demonstrated after an IV injection of titrated nimodipine in the rat.

The increase in peripheral blood flow is less pronounced than in cerebral blood flow after the same dose investigated. In normotensive rats, nimodipine has considerably less tendency to cause a fall in blood pressure than other dihydropyridine calcium channel blockers (eg, nifedipine and nicardipine). In addition to its dilating effect on the brain vessels in normal animals, the drug prevents the cerebrovascular damage induced by transitory ischemia, by electroshock, anoxia, or hypoxia.

In cats, impaired reperfusion of the brain due to a 7-minute global cerebral ischemia was completely prevented by the prophylactic administration of an oral dose of 1 mg/kg and partially improved by an oral dose of 0.5 mg/kg. The postischemic mortality of the animals was drastically reduced by nimodipine. Nimodipine was also effective when administered after the ischemic episode.

In dogs, impaired reperfusion of the brain due to temporary ligation of the aorta was also prevented by nimodipine. The cerebral blood flow in the delayed postischemic hypoperfusion period was nearly doubled by the prophylactic administration of 10 µg/kg IV nimodipine followed by an infusion of 1 µg/kg/min for two hours prior to the ischemic episode.

The effect of nimodipine was studied on cerebral vasospasm after experimental subarachnoid hemorrhage induced by intracisternal injection of autologous blood in dogs and cats. Angiographic measurements of the cross-sectional areas of the basilar and vertebral arteries of anaesthetized dogs demonstrated that 0.28 mg/kg sublingual nimodipine reversed the acute cerebral spasm. This occurred without a marked drop in blood pressure (maximum 10% reduction in systolic blood pressure). In a similar study in anaesthetized cats where pial vessel diameters were measured continuously by a Vidicon camera system, 0.01 and 0.1 mg/kg nimodipine IV also reversed acute cerebral spasm. The effect of the 0.01 mg/kg dose was more pronounced on pial vessels greater than 100 µm in diameter than on those less than 100 µm, whereas the opposite occurred after 0.1 mg/kg nimodipine. Mean arterial blood pressure was reduced by a maximum of 39 mm Hg, 1 minute after injection of 0.01 mg/kg, and subsequently blood pressure gradually returned toward control values. The maximum reduction in mean arterial blood pressure of 60 mm Hg, 1 minute after injection of 0.1 mg/kg was only slightly attenuated over the 30 minute postnimodipine observation period.

### **Animal Pharmacokinetics**

In rats and dogs [<sup>14</sup>C]-labelled nimodipine was absorbed rapidly and completely after oral administration. The maximum plasma concentration was reached after 20 to 60 minutes in rats and 2 to 3 hours in dogs. After maximum plasma concentrations were reached, the radioactivity was eliminated from the plasma with half-lives of approximately 40 minutes, 8 hours, and 3 days in the rat and 8 hours and 9 days in the dog. A strong first-pass effect was found in rats, and only 1% of unchanged substance was present in the plasma 30 minutes after oral administration. In dogs only 7% of the unchanged substance was found 90 minutes after oral administration.

In rats and dogs, 96% to 98% of unchanged active nimodipine was bound to plasma protein. The highest concentrations of nimodipine labelled with [<sup>14</sup>C] were found in the liver and the lowest concentrations in the brain.

Absence of unchanged substance in urine and bile shows that nimodipine was completely eliminated by biotransformation. The excretion of metabolites in both rats and dogs was predominantly in the bile. Eighty percent of [<sup>14</sup>C] activity administered was found in the feces and twenty percent in the urine.

In the rat, approximately 0.1% of the activity was found in the animal 10 days after oral administration of [<sup>14</sup>C]-labelled nimodipine. For the dog, corresponding residual values after 9 days were approximately 0.5% of the administered activity.

## TOXICOLOGY

### Acute Toxicity

The acute toxicity of nimodipine was studied in mice, rats, rabbits, and dogs after oral and intravenous administration. Nimodipine had low toxicity in all four species with acute median oral lethal doses ranging from 1000 to 6600 mg/kg.

**Table 6: Preclinical Toxicity Results Following Nimodipine Administration via Oral or Intravenous Route**

Species	Sex	Route of Administration	LD50 mg/kg	Confidence Limits (P = 0.05)
mouse	m	oral	3562	(2746-4417)
mouse	m	IV	33	(28-38)
rat	m	oral	6599	(5118- 10033)
rat	m	IV	16	(14-18)
rabbit	f	oral	app. 5000	-
rabbit	f	IV	app 2.5	-
dog	m/f	oral	1000-2000	-
dog	m/f	IV	app 4.5	-

Oral administration caused mild cyanosis, reduced motility, and gasping respiration in mice and rats. Intravenous administration produced these symptoms of intoxication, accompanied by tonic-clonic spasms and extension spasms in all the animal species studied.

### Subacute Toxicity Studies

In subacute toxicity studies of 3 months duration, oral doses up to 100 mg/kg/day were well tolerated in rats and rhesus monkeys. In dogs, a dose up to 3 mg/kg/day was nontoxic. 10 mg/kg/day caused intolerance reactions, retardation of growth, and pathological changes in P and T waves in the ECG.

Male rats tolerated IV nimodipine at dosages of 0.06 and 0.2 mg/kg/day and female rats tolerated dosages of 0.06, 0.2, and 0.6 mg/kg/day. No signs of impairment were noted at these dosages. Nimodipine administered by intravenous drip for 8 hours a day over a period of 4 weeks, at a dose of 150 µg /kg/H, was well tolerated by beagles, and no signs of local or systemic damage were observed.

### **Chronic Toxicity Studies**

In a dog study of one year duration, oral doses of 2.5 mg/kg of nimodipine were well tolerated. At oral doses of 6.25 mg/kg of nimodipine, 3 of 8 animals showed ST-segment depression on the electrocardiograms as a manifestation of local disturbance of the blood flow. However, the histopathological examination did not show any indication of myocardial damage.

### **Reproduction Studies**

Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidence of malformations and stunted fetuses were increased at oral doses (by gavage) of 1 and 10 mg/kg/day administered 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 were 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 at day 20 of pregnancy or day 21 postpartum were associated with higher incidence of skeletal variation, stunted fetuses, and stillbirths, but no malformations.

Nimodipine did not impair the fertility and general reproductive performance of rats following oral doses of up to 30 mg/kg/day and did not impair 1st and 2nd generation animals.

### **Carcinogenicity Studies**

In a two-year study, higher incidence of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing nimodipine equivalent to 91 to 121 mg/kg/day, than in placebo controls. The differences were, however, not statistically significant and the higher rates of lesions were well within historical control range for these tumors in the Wistar rat strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study, but the high dose of drug in the diet, equivalent to doses of nimodipine as high as 546 to 774 mg/kg/day, shortened the life expectancy of the animals.

### **Mutagenicity Studies**

Mutagenic studies with nimodipine were negative when tested by the Salmonella/microsome test for point mutagenic effects, and by the micronucleus test and by the dominant lethal test.

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## PART III: CONSUMER INFORMATION

### PrNIMOTOP® Tablets

nimodipine tablets Bayer Standard

*This leaflet is Part 3 of a three-part "Product Monograph" published when NIMOTOP Tablets was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NIMOTOP Tablets. Contact your doctor or pharmacist if you have any questions about the drug.*

#### ABOUT THIS MEDICATION

##### **What the medication is used for:**

NIMOTOP Tablets are used for the treatment subarachnoid hemorrhage (medical term for bleeding inside the head) and help to prevent brain damage that may result from the bleeding.

##### **What it does:**

Following subarachnoid hemorrhage (medical term for bleeding inside the head), the blood vessels may go into spasm. This may result in inadequate circulation in the affected areas of the brain and thus damage the nervous system. NIMOTOP Tablets are used to prevent and, if necessary, to treat such damage.

##### **When it should not be used:**

Do not take NIMOTOP Tablets:

- if you have suffered from a head injury resulting in a traumatic subarachnoid hemorrhage
- during or within one month of a heart attack
- if you suffer from angina and notice an increase in the frequency and severity of attacks
- if you are taking the antibiotic rifampin or the antiepileptics phenobarbital, phenytoin or carbamazepine as the effect of NIMOTOP Tablets may be reduced
- if you are breastfeeding
- if you are allergic (hypersensitive) to nimodipine or to any of the ingredients in this product. The ingredients are listed in the "**What the nonmedicinal ingredients are**" section of this leaflet

##### **What the medicinal ingredient is:**

The active substance is nimodipine

##### **What the nonmedicinal ingredients are:**

Crospovidone, ferric oxide yellow, hypromellose, macrogol, magnesium stearate, maize starch, microcrystalline cellulose, povidone, and titanium dioxide

##### **What dosage forms it comes in:**

Film-coated tablets, 30 mg

#### WARNINGS AND PRECAUTIONS

BEFORE you use NIMOTOP Tablets, talk to your doctor or pharmacist if you have or have had any of the following conditions:

- have hypotension (systolic blood pressure below 100 mmHg)
- have been told that you have cerebral edema or severely raised intracranial pressure
- have a history of liver disease
- have a history of heart disease
- may be pregnant or are breastfeeding

#### INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with NIMOTOP Tablets include:

- drugs used for the treatment of epilepsy (eg, phenytoin, carbamazepine, phenobarbital, valproic acid); tuberculosis (eg, rifampin) and HIV infections (eg, ritonavir)
- antibiotics (eg, erythromycin) for infectious disease
- antihypertensive drugs (for high blood pressure), including other calcium channel blockers
- drugs used to treat fungal infections (eg, ketoconazole), unless they are applied only to the skin
- antidepressants (eg, fluoxetine, nortriptyline)
- drugs used to treat indigestion (eg, cimetidine)
- herbal remedy St. John's Wort (primarily used for the treatment of depressive moods)

If you are taking any of the above drugs, remind your doctor before taking NIMOTOP tablets. If necessary, a reduction in the nimodipine dose should be considered.

NIMOTOP Tablets should not be taken at the same time as grapefruit juice, or near the time of eating grapefruit. This is because grapefruit juice is known to increase the blood levels of the active ingredient, nimodipine.

*This is not a complete list of possible drug interactions with NIMOTOP Tablets. Talk to your doctor for more information about drug interactions.*

See also **ABOUT THIS MEDICATION: When it should not be used**, and **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**.

## PROPER USE OF THIS MEDICATION

### Usual dose

For the management of neurological deficits following subarachnoid hemorrhage (SAH), therapy with NIMOTOP Tablets should start as soon as possible or within 4 days of the diagnosis of SAH.

The recommended dosage of NIMOTOP Tablets is 60 mg (two tablets of 30 mg) administered orally every 4 hours for 21 consecutive days after diagnosis of SAH. Doses up to 90 mg every 4 hours have been used in some patients, although the safety of higher doses in severely ill patients has not been well established.

The tablets should be swallowed whole with plenty of fluid (preferably a glass of water), independently of meal times. Grapefruit juice should be avoided. It is recommended that the tablets are not taken while lying down.

### Children and Adolescents

Do not give NIMOTOP Tablets to patients under 18 years of age. There is not enough information on their use in children and adolescents.

### Pregnancy and Breastfeeding

If you are pregnant or are planning a family, tell your doctor before taking NIMOTOP Tablets. Investigations have not been carried out into the damaging effects of NIMOTOP during pregnancy. NIMOTOP should therefore only be taken during pregnancy after careful consideration of the benefits and potential risks arising from the severity of the clinical situation.

Since nimodipine (the active ingredient in NIMOTOP Tablets) may pass into breast milk, breastfeeding should be discontinued while taking this drug.

### Overdose

Symptoms of acute overdosage to be anticipated are marked lowering of the blood pressure, an irregular heart beat, flushing, headache, digestive upset and nausea.

In the event of acute overdose, discontinue use of NIMOTOP Tablets immediately and contact your doctor or your regional Poison Control Centre immediately.

### Missed Dose

If you have forgotten to take a dose, take it as soon as you remember. Carry on with the remaining tablets at the normal four-hour intervals.

Do not take a double dose to make up for a forgotten tablet.

### Stopped Treatment

You should always consult your doctor before deciding to interrupt or stop the course of NIMOTOP Tablet treatment (eg, on account of side effects) since NIMOTOP Tablets prevent the development of serious neurological deficits.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, NIMOTOP can cause side effects, although not everybody gets them.

The most common side effects seen with NIMOTOP are allergic reaction (eg, rash), decreased blood pressure, irregular heartbeat, headache, sweating, flushing, nausea.

There is a possibility that you may feel dizzy; if you are affected you should not drive or operate machinery.

Please inform your doctor or pharmacist if you experience any side effects. If necessary, your doctor may reduce or stop treatment with NIMOTOP Tablets.

You should be aware that prescription medications carry some risks and that all possible risks may not be known at this stage.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom/ Effect	Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical treatment
	Only if severe	In all cases	
<b>Common</b>	Low blood pressure (lightheadedness, dizziness, and/or fainting)		✓
	Allergic reactions: difficulty breathing or swallowing, rash or hives (redness, intense itching), swelling of face, throat, tongue, lips, eyes, hands, feet, ankles, lower legs)		✓
	Localized swelling, swelling in your limbs		✓
	Increased frequency and looseness in bowel movement		✓
	Unease and discomfort in the stomach with an urge to vomit		✓
<b>Uncommon</b>	Headache, pain in the neck and/or upper back		✓
	Yellowing of the skin or eyes (jaundice)		✓
	Anemia (exceptional weakness, paleness, dizziness, headache)		✓

*This is not a complete list of side effects. For any unexpected effects while taking NIMOTOP Tablets, contact your doctor or pharmacist.*

**HOW TO STORE IT**

NIMOTOP tablets should be stored in the original packaging between 15°C and 30°C. Protect from humidity.

Keep out of reach of children.

Medications should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medications you no longer require. These measures will help to protect the environment.

**REPORTING SUSPECTED SIDE EFFECTS**

Canada Vigilance Program:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    - Canada Vigilance Program
    - Health Canada
    - Postal Locator 0701E
    - Ottawa, Ontario
    - K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or [canada.medinfo@bayer.com](mailto:canada.medinfo@bayer.com).

This document plus the full product monograph, prepared for health professionals can be found at: <http://www.bayer.ca> or by contacting the manufacturer at the above-mentioned phone number and e-mail address.

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