

DATA SHEET

1. NIMOTOP®

Nimotop 10 mg/ 50 mL concentrated intravenous infusion solution
Nimotop 30 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Each bottle of 50 mL Nimotop concentrated intravenous infusion solution contains 10mg nimodipine in 50 mL alcoholic solvent.

NIMOTOP TABLETS

Each Nimotop tablet contains 30mg nimodipine.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Clear intravenous solution for infusion.

NIMOTOP TABLETS

Round, convex, yellow film coated tablets marked with "SK" on top and the Bayer cross on the bottom.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Prophylaxis and treatment of ischaemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorrhage of aneurysmal origin. Patients should be in good neurological condition post-ictus.

NIMOTOP TABLETS

After a preceding infusion of Nimotop concentrated intravenous infusion solution, for:-
Prophylaxis and treatment of ischaemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorrhage of aneurysmal origin. Patients should be in good neurological condition post-ictus.

4.2 Dose and method of administration

Dose

Unless otherwise prescribed, the following dose is recommended:

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Intravenous infusion

At the beginning of treatment 1mg/hr nimodipine (= 5 mL Nimotop concentrated intravenous infusion solution/h) for 2 hours (about 15µg/kg body weight/h). If this is well tolerated, and particularly if there is no marked reduction in blood pressure, the dose is increased after 2 hours to 2mg/hr nimodipine (= 10 mL Nimotop concentrated intravenous infusion solution/h) (about 30µg/kg body weight/h). Patients whose body weight is appreciably below 70kg or who have labile blood pressure should be started with a dose of 0.5mg/hr nimodipine (= 2.5 mL Nimotop concentrated intravenous infusion solution/h).

Intracisternal instillation

During surgery a freshly prepared dilute solution of nimodipine (20 mL of dilute solution of Nimotop: 1 mL of Nimotop concentrated intravenous infusion solution and 19 mL of Ringer solution) warmed up to blood temperature may be instilled intracisternally. This dilution must be used immediately after preparation.

NIMOTOP TABLETS

The recommended procedure is administration of Nimotop concentrated intravenous infusion solution for 5 – 14 days, followed by a daily dose of 6 x 2 Nimotop tablets (6 x 60mg nimodipine).

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. In such cases, the dose should be reduced. If necessary, discontinuation of the treatment should be considered.

Upon co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers a dose-adaptation may be necessary (see Section 4.5).

Method of 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. It should be given via

a three-way stopcock together with either glucose 5%, sodium chloride 0.9%, lactated Ringer's solution, lactated Ringer's solution with magnesium, dextran 40 solution or HAES (poly(O-2-hydroxyethyl) starch 6% in a ratio of about 1:4 (Nimotop: co-infusion). Also mannitol, human albumin or blood are suitable for co-infusion.

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

Nimotop solution must not be added to an infusion bag or bottle and must not be mixed with other medicines. Administration of Nimotop should be continued during anaesthesia, surgery and angiography.

The three-way stopcock should be used to connect the Nimotop polyethylene tube with the co-infusion line and the central catheter.

NIMOTOP TABLETS

Administration of Nimotop tablets is recommended for about 7 days after the end of 5 – 14 days infusion therapy with Nimotop concentrated intravenous infusion solution.

In general, the tablets should be swallowed whole with a little liquid, independent of meal time. Grapefruit juice is to be avoided (see Section 4.5). The interval between successive doses must not be less than 4 hours.

Duration of administration

Prophylactic Use

Intravenous therapy should be started no later than 4 days after the haemorrhage, and be continued during the period of maximum risk of vasospasm, i.e. up to 10-14 days after the haemorrhage.

If during the prophylactic administration of Nimotop, the source of the haemorrhage is treated surgically, intravenous treatment with Nimotop 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 of 6 x 60mg nimodipine daily at four hourly intervals for about a further 7 days.

Therapeutic Use

If ischaemic neurological disturbances caused by vasospasm after aneurysmal subarachnoid haemorrhage are already present, treatment should be started as early as possible and be continued for at least 5 days up to a maximum of 14 days.

Thereafter, oral administration of 6 x 60mg Nimotop tablet per day at four hourly intervals for 7 days is recommended.

If during therapeutic administration of Nimotop, the source of the haemorrhage is treated surgically, intravenous treatment with Nimotop should be continued post-operatively for at least 5 days.

4.3 Contraindications

Hypersensitivity to nimodipine or any of the excipients.

The use of nimodipine in combination with rifampicin is contraindicated as efficacy of nimodipine tablets may be significantly reduced when concomitantly administered with rifampicin (see Section 4.5).

The concomitant use of oral nimodipine and the antiepileptic medicines phenobarbital, phenytoin or carbamazepine is contraindicated as efficacy of nimodipine tablets may be significantly reduced (see Section 4.5).

4.4 Special warnings and precautions for use

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

Caution is required in patients with hypotension (systolic blood pressure lower than 100 mm Hg).

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

Nimotop concentrated intravenous infusion solution contains 23.7 vol% ethanol (alcohol), i.e. up to 50 g per daily dose (250 mL). 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 medicinal product may alter the effects of other medicines (see Section 4.5).

Nimodipine is metabolised via the cytochrome P450 3A4 system. Medicines that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nimodipine (see Section 4.5).

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

4.5 Interaction with other medicines and other forms of interaction

Medicines that affect nimodipine

Nimodipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Medicines 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 medicines:

Rifampicin

From experience with other calcium antagonists rifampicin is expected to accelerate the metabolism of nimodipine due to enzyme induction. Thus, efficacy of nimodipine may be significantly reduced when concomitantly administered with rifampicin. The use of nimodipine in combination with rifampicin is therefore contraindicated (see Section 4.3).

Cytochrome P450 3A4 system-inducing anti-epileptic medicines, such as phenobarbital, phenytoin or carbamazepine

Previous chronic administration of the antiepileptic medicines, phenobarbital, phenytoin or carbamazepine markedly reduces the bioavailability of orally administered nimodipine. Therefore, the concomitant use of oral nimodipine and these antiepileptic medicines is contraindicated (see Section 4.3).

Upon co-administration with the following inhibitors of the cytochrome P450 3A4 system, blood pressure should be monitored and, if necessary, an adaptation in the nimodipine dose should be considered (see 4.2).

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 Section 4.4).

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. Medicines 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 Section 4.4).

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 Section 4.4).

Nefazodone

No formal studies have been performed to investigate the potential interaction between nimodipine and nefazodone. This antidepressant medicine 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 Section 4.4).

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 Section 4.4).

Cimetidine

The simultaneous administration of the H₂-antagonist cimetidine can lead to an increase in the plasma nimodipine concentration (see Section 4.4).

Valproic acid

The simultaneous administration of the anticonvulsant valproic acid can lead to an increase in the plasma nimodipine concentration (see Section 4.4).

Effects of nimodipine on other medicines

Blood pressure lowering medicines

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.

Simultaneous intravenous administration of β -blockers may lead to mutual potentiation of negative inotropic action, potentially leading to decompensated heart failure in some cases.

Zidovudine

In a monkey study simultaneous administration of anti-HIV medicine, zidovudine intravenous and nimodipine bolus intravenous resulted in a significantly higher AUC for zidovudine, whereas the distribution volume and clearance were significantly reduced.

Renal function can deteriorate if potentially nephrotoxic medicines (e.g. aminoglycosides, cephalosporins, furosemide) are given simultaneously, and also in patients whose renal function is already impaired. Renal function must be monitored carefully in such cases, and if a deterioration is found discontinuation of the treatment should be considered.

Drug-food interactions

Grapefruit juice

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of dihydropyridine calcium antagonists together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nimodipine due to a decreased first pass metabolism or reduced clearance.

As a consequence, the blood pressure lowering effect may be increased. After intake of grapefruit juice this effect may last for at least 4 days after the last ingestion of grapefruit juice.

Ingestion of grapefruit / grapefruit juice is therefore to be avoided while taking nimodipine (see Section 4.2).

Since Nimotop concentrated intravenous infusion solution contains 23.7% vol-% of alcohol, interactions with alcohol-incompatible medicines should be taken into consideration (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

No adequate and well controlled studies are available in pregnant women. If Nimotop is to be administered during pregnancy, the benefits and the potential risks must therefore be carefully weighed according to the severity of the clinical picture.

Lactation

Nimodipine and its metabolites have been shown to appear in breast 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 medicine.

Fertility

In single cases of *in vitro* fertilisation, calcium antagonists have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function.

4.7 Effect on ability to drive and use machines

In principle the ability to drive and use machines can be impaired with the possible occurrence of dizziness. In using Nimotop concentrated intravenous infusion solution, this influence will generally not be of importance.

4.8 Undesirable effects

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

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

Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)

Table 1. ADRs reported in patients from clinical trials

System Organ Class (MedDRA)	Uncommon	Rare
Blood and lymphatic system disorders	Thrombocytopenia	
Immune system disorders	Allergic Reaction Rash	
Nervous system disorders	Headache	
Cardiac disorders	Tachycardia	Bradycardia
Vascular disorders	Hypotension Vasodilatation	
Gastrointestinal disorders	Nausea	Ileus

Hepatobiliary disorders		Transient increase in liver enzymes
General disorders and administration site conditions		Injection and infusion site reactions Infusion site (thrombo-) phlebitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

<https://pophealth.my.site.com/carmreportnz/s/>

4.9 Overdose

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

In the event of acute overdosage, treatment with Nimotop must be discontinued immediately. Emergency measures should be governed by the symptoms. Activated charcoal may reduce absorption of nimodipine if given one or two hours after ingestion. 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C08 CA06

Nimodipine is a calcium antagonist belonging to the 1,4-dihydropyridine group. The contractile processes of smooth muscle cells are dependent upon calcium ions, which enter these cells during depolarisation 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. This may be 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 haemorrhage (SAH) patients.

Nimodipine, has a predilective cerebral antivasoconstrictive and antiischaemic activity. Vasoconstrictions provoked *in vitro* by various vasoactive substances (e.g. serotonin, prostaglandins, and histamine) or by blood and blood degradation products can be

prevented or eliminated by nimodipine. Nimodipine also has neuropharmacological and psychopharmacological properties.

Investigations in patients with acute cerebral blood flow disturbances have shown that nimodipine dilates the cerebral blood vessels and promotes cerebral blood flow. The increase in perfusion is as a rule greater in previously damaged or underperfused brain regions than in healthy regions. In patients with subarachnoid haemorrhage the ischaemic neurological damage and the mortality rate are significantly reduced by nimodipine.

5.2 Pharmacokinetic properties

Absorption

The orally administered active substance nimodipine is practically completely absorbed. The unchanged active substance and its early "first pass" metabolites are detected in plasma as little as 10 –15 min after ingestion of the tablet. Following multiple dose oral administration (3 x 30 mg/day), the peak plasma concentrations (C_{max}) are 7.3 – 43.2 ng/mL in elderly individuals, these being reached after 0.6 – 1.6 hours (T_{max}). Single dosing of 30mg and 60mg in young subjects results in mean peak plasma concentrations of 16 ± 8 ng/mL and 31 ± 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 (90mg).

Using continuous infusions of 0.03 mg/kg/hour, 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 min and about 60 min. 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.

Protein binding and distribution

Nimodipine is 97 - 99% bound to plasma proteins. In animal experiments radioactivity from [^{14}C]-nimodipine passed the placental barrier. Similar distribution is likely for humans though there is no experimental evidence in this area. Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. Parent medicine concentrations determined in human milk were of the same magnitude as corresponding maternal plasma concentrations.

After oral and intravenous administration nimodipine can be detected in the CSF in concentrations about 0.5% of the measured plasma concentrations. These correspond roughly to the free concentration in plasma.

Metabolism, elimination and excretion

Nimodipine is eliminated metabolically via the cytochrome P450 3A4 system, mainly by dehydrogenation of the dihydropyridine ring and oxidative O-demethylation. Oxidative ester cleavage, hydroxylation of the 2- and 6-methyl groups, and glucuronidation as a conjugation reaction are further important metabolic steps. The three primary

metabolites occurring in plasma show no or only therapeutically unimportant residual activity.

Effects on liver enzymes by induction or inhibition are unknown. In humans the metabolites are excreted about 50% renally and 30% in the bile.

The elimination kinetics are linear. The half-life for nimodipine is between 1.1 and 1.7 hours. The terminal half-life of 5 - 10 hours has no significance in establishing the dosage interval.

Bioavailability

Attributed to the extensive first-pass metabolism (about 85 - 95%) the absolute bioavailability is 5 - 15%.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenicity and male and female fertility. In pregnant rats, doses of 30 mg/kg/day and higher inhibited fetal growth and resulted in reduced fetal weights. At 100 mg/kg/day embryoletality occurred. No evidence of teratogenicity was observed. In rabbits, no embryotoxicity and teratogenicity occurred at doses up to 10 mg/kg/day. In one peri-postnatal study in rats, mortality and delayed physical development were observed at doses of 10 mg/kg/day and higher. The findings were not confirmed in subsequent studies.

Acute toxicity

Species	Sex	Route of Administration	LD ₅₀ mg/kg	Confidence interval for $p \leq 0.05$
Mouse	Male	per os	3562	(2746 - 4417)
Mouse	Male	Intravenous	33	(28 - 38)
Rat	Male	per os	6599	(5118 - 10003)
Rat	Male	Intravenous	16	(14 - 18)
Rabbit	Female	per os	Approx. 5000	
Rabbit	Female	Intravenous	Approx. 2.5	
Dog	Both	per os	Between 1000 & 2000	
Dog	Both	Intravenous	Approx. 4.5	

The difference between the LD₅₀ values after oral and intravenous administration indicates that after high dose oral administration, in the form of a suspension, the absorption of the active substance is either incomplete or delayed. Symptoms of poisoning were observed only in mice and rats. These symptoms included: slight cyanosis, severely reduced motility and gasping respiration. After intravenous administration these signs of poisoning were observed in all the species studied, with the addition of tonic-clonic convulsions.

Subacute Tolerability Studies over 3 and 4 weeks after Intravenous Administration

Groups of 10 male and 10 female Wistar rats were given nimodipine over a period of 3 weeks in doses of 0.06, 0.2 and 0.6 mg/kg. The substance was emulsified in a 10% Cremophor solution and injected in the caudal vein. All animals survived the period of treatment without any clinical symptoms. Up to a dose of 0.6mg/kg the haematological tests and urinalysis did not indicate any toxic effects. Autopsies performed on experimental animals after the end of treatment showed that the kidneys of the male rats were significantly heavier. However, histopathological examination of the kidneys failed to reveal any pathological findings. No changes were found in other organ systems. Local tolerability in the region of the injection sites was also good. Ignoring the differences between the sexes, it can be said that in every case doses of up to 0.2 mg/kg, administered intravenously once a day for a period of 3 weeks, were tolerated without toxic effects.

Systemic and local tolerabilities were investigated in a 4-week toxicity study with intravenous administration to dogs. The substance was administered in doses of 0.02, 0.06 and 0.2 mg/kg in a mixture of ethanol and polyethylene glycol 400. Clinical and laboratory tests as well as macroscopic and histopathological examinations failed to reveal any damage caused by the substance.

In another study 2 male and 2 female beagles were given 150 µg nimodipine/kg/hr in the form of an intravenous drip for 8 hours a day 7 times a week over a total period of 4 weeks. The substance was dissolved in the ethanol/polyethylene glycol 400 solvent mixture as bypass to Ringer solution; 4 control animals were given infusions of the corresponding amounts of the solvent mixture alone. Nimodipine was tolerated without the development of clinical symptoms. In a second dog subacute study, a dose of 1.2 mg/kg/day was given by intravenous infusion for 8 hours daily (1.5 mL/kg/hr) for 4 weeks which caused drops in blood pressure and increase in heart rate an hour after infusion. The haematological and biochemical test and urinalyses did not indicate any alterations caused by the test substance. Also macroscopic and histopathological examinations did not yield any pathological findings.

Chronic Tolerability Studies

Rats were treated with nimodipine mixed with the feed, in daily doses of up to about 90mg/kg/day for 2 years. Doses up to 15 mg/kg/day were tolerated by both males and females without any discernible damage. There was no evidence of oncogenic effects of the substance. The above doses of nimodipine were given to mice as an admixture to the food for 21 months. This study also produced no evidence of any tumorigenic activity.

In a one-year study on dogs the systemic tolerability of doses of up to 6.25 mg nimodipine/kg/day was investigated. Doses up to 2.5 mg/kg proved harmless, while 6.25 mg/kg gave rise to electrocardiographic changes due to disturbances in myocardial blood flow. However, no histopathological alterations in the heart were found at this dose.

Studies on Reproduction Toxicology

Fertility Studies in Rats

The fertility of male and female rats and subsequent generations was unimpaired at doses up to 30 mg/kg/day.

Embryotoxicity Studies

Administration of 10 mg/kg/day to pregnant rats during embryogenesis showed no harmful effects. Doses of 30 mg/kg/day and more inhibited growth, causing reduced fetal weight, and at 100 mg/kg/day increased numbers of embryos died *in utero*. No teratogenic effects were observed.

Embryotoxicity studies in rabbits with doses up to 10 mg/kg/day p.o. yielded no evidence of teratogenic or other embryotoxic effects.

Perinatal and Postnatal Development in Rats

To investigate perinatal and postnatal development, studies were conducted in rats with doses up to 30 mg/kg/day. In one study increased perinatal and postnatal mortality and delayed physical development were observed with 10 mg/kg/day and more. These findings were not confirmed in subsequent studies.

Special Tolerability Studies

Cancerogenicity Studies

A lifetime study in which rats received nimodipine at doses of up to 1800 ppm (about 90 mg/kg/day) in their feed for 2 years yielded no evidence of an oncogenic potential. Similarly, a long-term study in which mice received 500 mg/kg/day p.o. for 21 months produced no evidence that nimodipine has an oncogenic potential.

Mutagenicity

Nimodipine has been the subject of extensive genotoxicity testing. All tests for the induction of mutagenic and chromosomal mutations were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Ethanol 96%, macrogol 400, sodium citrate dihydrate, citric acid, water for injection.

NIMOTOP TABLETS

Povidone, microcrystalline cellulose, maize starch, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide, iron oxide yellow.

6.2 Incompatibilities

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Since the active substance of Nimotop concentrated intravenous infusion solution is absorbed by polyvinyl-chloride (PVC), only polyethylene (PE) infusion tubing may be used.

The active substance of Nimotop concentrated intravenous infusion solution is slightly light-sensitive therefore its use in direct sunlight should be avoided. If direct exposure to sunlight is unavoidable during an infusion, black, brown, yellow or red glass syringes and connecting tubing should be used, or the infusion pump and the tubing be protected by opaque wrappings. However, no special protective measures need be taken for up to 10 hours if Nimotop is being given in diffuse daylight or in artificial light.

6.3 Shelf life

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

36 months

NIMOTOP TABLETS

Nimotop tablets in blister packs (PP/Al) – 60 months.

Nimotop tablets in blister packs (PA/Al/PVC/Al or PVC/PVDC/Al) – 48 months.

6.4 Special precautions for storage

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

Store below 25°C. Protect from direct sunlight if the bottle is removed from the carton.

NIMOTOP TABLETS

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

Blister pack (PP/Al)	- Store below 25°C
Blister pack (PVC/PVDC/Al)	- Store below 25°C
Blister pack (PA/Al/PVC/Al)	- Store below 30°C

Not all packaging material types may be marketed. Refer to medicine carton for storage instructions.

6.5 Nature and contents of container

NIMOTOP CONCENTRATED INTRAVENOUS INFUSION SOLUTION

50 mL solution in a vial (glass, brown) with a stopper (chlorobutyl rubber) in pack size of 1 (sold in quantities of 5).

Each pack contains:

- One vial of Nimotop
- One polyethylene infusion line

NIMOTOP TABLETS

Pack size of 100 film coated tablets.

Tablets are packed in foil blisters of:
polypropylene/aluminium or polyvinyl chloride/polyvinylidene chloride/aluminium or
polyamide/aluminium/polyvinyl chloride/ aluminium.

Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
P O Box 2825
Shortland Street
Auckland 1140
New Zealand

Free phone: 0800 233 988

9. DATE OF FIRST APPROVAL

17 December 1992

10. DATE OF REVISION OF THE TEXT

10 January 2024

Summary table of changes

Section changed	Summary of new information
4.9	Deletion of gastric lavage.
6.3	Change to shelf life for tablets packed in PVC/PVDC/Al blisters.