SCHEDULING STATUS: S3

PROPRIETARY NAMES AND DOSAGE FORMS:

NIMOTOP® 30 mg	Film-coated tablets
NIMOTOP® IV	Solution

COMPOSITION:

Each NIMOTOP 30 mg film-coated tablet contains 30 mg nimodipine.
Other ingredients: crospovidone, ferric oxide yellow, hypromellose 15 cP, macrogol 4000, magnesium stearate, maize starch, microcrystalline cellulose, povidone 25, purified water, titanium dioxide.

NIMOTOP IV: nimodipine 10 mg/50 ml – contains 25 % v/v ethanol.
Other ingredients: citric acid anhydrous, ethanol 96 %, macrogol 400, sodium citrate**,** water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1 Vasodilators, hypotensive medicines

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Nimodipine is a calcium channel antagonist of the dihydropyridine group. Nimodipine acts particularly on cerebral blood vessels and dilates the cerebral blood vessels.

Pharmacokinetic properties:

Absorption:

After oral administration nimodipine is practically completely absorbed, but undergoes extensive first pass metabolism, with a resultant bioavailability of 5 to 15 %.

The distribution volume (V_{ss}, 2-compartment model) for IV administration is calculated to be 0,9 to 1,6 l/kg body weight. The total (systemic) clearance is 0,6 to 1,9 l/h/kg.

Protein binding and distribution:

Nimodipine is 97 to 99 % bound to plasma proteins.

Metabolism, elimination and excretion:

Nimodipine is eliminated metabolically via the cytochrome P450 3A4 system. It is excreted in faeces via the bile, and in urine. The terminal elimination half-life is about 9 hours.

INDICATIONS:

NIMOTOP IV:

Prophylaxis and treatment of ischaemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorrhage of aneurysmal origin.

NIMOTOP 30 mg:

After an infusion of NIMOTOP IV, for prophylaxis and treatment of ischaemic neurological deficits caused by cerebral vasospasm following subarachnoid haemorrhage of aneurysmal origin.

CONTRA-INDICATIONS:

Safety during pregnancy and lactation has not been established (see “Pregnancy and lactation”).
In patients with severely impaired liver function, dosage reduction may be required and discontinuation of treatment should be considered, if hypotension occurs.

The use of NIMOTOP in combination with rifampicin is contra-indicated as efficacy of NIMOTOP tablets could be significantly reduced when concomitantly administered with rifampicin (see "Interactions”).

The concomitant use of NIMOTOP 30 mg tablets and the antiepileptic medicines phenobarbital, phenytoin or carbamazepine is contra-indicated as efficacy of NIMOTOP 30 mg tablets could be significantly reduced (see "Interactions”).

Known hypersensitivity to nimodipine or any of the excipients.

WARNINGS AND SPECIAL PRECAUTIONS:

NIMOTOP 30 mg tablets should not be administered concomitantly with NIMOTOP IV solution.

NIMOTOP 30 mg tablets and NIMOTOP IV solution must be used with care when cerebral oedema or severely raised intracranial pressure are present.

Although treatment with NIMOTOP 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 oedema). Caution is required in patients with hypotension (systolic blood pressure lower than 100 mmHg).

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

Patients with known renal disease and/or receiving nephrotoxic medicines, should have renal function monitored closely during intravenous treatment with NIMOTOP IV solution.

NIMOTOP 30 mg tablets:

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 "Interactions”).

Medicines, which are known inhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nimodipine include (see “Interactions”):

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

NIMOTOP IV contains up to 50 g of alcohol 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 “Interactions”).

NIMOTOP IV solution reacts with polyvinylchloride (PVC). Polyethylene or polypropylene are the recommended plastic materials to be used during NIMOTOP infusion.

NIMOTOP IV solution is compatible with glass infusion bottles and infusion packs made of polyethylene. NIMOTOP IV solution is incompatible with infusion bags and any administration sets made of PVC.

Polyethylene tubes are supplied with NIMOTOP IV solution, and these must not be substituted.

Effects on the ability to drive and use machines:
The ability to drive and use machines can be impaired due to the possible occurrence of dizziness when taking NIMOTOP tablets.

INTERACTIONS:

NIMOTOP 30 mg tablets:

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 induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of NIMOTOP.

The extent as well the duration of interactions should be taken into account when administering NIMOTOP 30 mg tablets together with the following medicines:

Rifampicin:

From the experience with other calcium antagonists it is expected that rifampicin accelerates the metabolism of NIMOTOP due to enzyme induction. Thus, efficacy of NIMOTOP could be significantly reduced when concomitantly administered with rifampicin. The use of NIMOTOP in combination with rifampicin is therefore contra-indicated (see "Contra-indications").

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 NIMOTOP. Therefore, the concomitant use of NIMOTOP and these antiepileptic medicines is contra-indicated (see "Contra-indications")

Upon co-administration with the following inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, an adaptation in the NIMOTOP dose should be considered (see "Dosage and directions for use"):

Macrolide antibiotics (e.g. erythromycin):

No interaction studies have been carried out between NIMOTOP and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 system and the potential for interaction cannot be ruled out at this stage. Therefore, macrolide antibiotics should not be used in combination with NIMOTOP (see "Warnings and Special Precautions").

Azithromycin, although structurally related to the class of macrolide antibiotic is void of CYP 3A4 inhibition.

Anti-HIV protease inhibitors (e.g. ritonavir):

No formal studies have been performed to investigate the potential interaction between NIMOTOP 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 NIMOTOP plasma concentrations upon co-administration with these protease inhibitors cannot be excluded (see "Warnings and Special Precautions").

Azole anti-mycotics (e.g. ketoconazole):

A formal interaction study investigating the potential of drug interaction between NIMOTOP 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 NIMOTOP 30 mg tablets, a substantial increase in systemic bioavailability of nimodipine due to a decreased first-pass metabolism cannot be excluded (see "Warnings and Special Precautions").

Nefazodone:

No formal studies have been performed to investigate the potential interaction between NIMOTOP 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 "Warnings and Special Precautions").

Quinupristin/dalfopristin:

Based on experience with other calcium-antagonists, co-administration of quinupristin/dalfopristin may lead to increased plasma concentrations of NIMOTOP (see "Warnings and Special Precautions").

Cimetidine:

The simultaneous administration of the H_2-antagonist cimetidine can lead to an increase in the plasma NIMOTOP concentration (see "Warnings and Special Precautions").

Valproic acid:

The simultaneous administration of the anticonvulsant valproic acid can lead to an increase in the plasma NIMOTOP concentration (see "Warnings and Special Precautions").

Effects of NIMOTOP on other medicines:

Blood pressure lowering medicines:

NIMOTOP may increase the blood pressure lowering effect of concomitantly used anti-hypertensives, such as:
- diuretics,
- β-blockers,
- ACE inhibitors,
- angiotensin receptor blockers,
- 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.

Medicine-food interactions:

NIMOTOP 30 mg tablets:

Grapefruit juice:

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of dyhydropyridine calcium antagonists such as NIMOTOP 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 NIMOTOP (see "Dosage and directions for use".

NIMOTOP 30 mg tablets and NIMOTOP IV solution:

Fluoxetine:

The steady-state concomitant administration of NIMOTOP 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 NIMOTOP and nortriptyline led to a slight decrease in nimodipine exposure with unaffected nortryptyline plasma concentrations.

Zidovudine:

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

NIMOTOP IV solution:

Simultaneous intravenous administration of β-blockers may lead to mutual potentiation of negative ionotropic action going as far as decompensated heart failure.

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 NIMOTOP should be considered.

Since NIMOTOP infusion solution contains alcohol, interactions with alcohol-incompatible medicines should be taken into consideration (see "Composition").

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

Pregnancy:

There are no adequate and well controlled studies in pregnant women.

Lactation:

Nimodipine and its metabolites have been shown to appear in human milk at concentrations of the same order of magnitude as corresponding maternal plasma concentrations. Breastfeeding mothers are advised not to breastfeed their babies when taking NIMOTOP.

Fertility:

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.

DOSAGE AND DIRECTIONS FOR USE:

NIMOTOP IV solution (may be used in lieu of tablets):

To penetrate the coated injection stoppers correctly, fine acute injection needles are recommended. DO NOT use large-core infusion needles, since this may result in cracked or bruised stoppers and the stoppers may be forced into the vial.

For the first two hours of treatment 1 mg of nimodipine i.e. 5 ml NIMOTOP IV solution, (about 15 µg/kg body mass), should be infused each hour. The dose should be increased after 2 hours to 2 mg nimodipine i.e. 10 ml NIMOTOP IV solution per hour (about 30 µg/kg body mass), providing no severe decrease in blood pressure is observed.

Patients of body mass less than 70 kg or with unstable blood pressure should be started on a dose of 0,5 mg nimodipine per hour (2,5 ml of NIMOTOP IV solution), or less if necessary.

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 or, 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 ”Interactions”).

NIMOTOP 30 mg tablets:

The recommended procedure is administration of NIMOTOP IV solution for 5 to 14 days, followed by a daily dose of two tablets at 4-hourly intervals, (total daily dose 360 mg), to be taken with water. Administration of NIMOTOP tablets should be continued to complete the total duration of NIMOTOP therapy started with the IV formulation, of 21 days.

In general, the tablets should be swallowed whole with a little liquid, independent of meal time. Grapefruit juice is to be avoided (see ”Interactions”).

Prophylactic administration:

Intravenous therapy should be started no later than 4 days (96 hours) 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 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 60 mg nimodipine daily at four-hourly intervals for a further 7 days.

Therapeutic administration:

If ischaemic neurological disturbances caused by vasopasm 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 60 mg NIMOTOP per day at four-hourly intervals for 7 days to complete the 21 day treatment period is recommended. Tablets may be substituted by NIMOTOP IV solution (dosage as above).

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.

NIMOTOP IV solution may be used with or without pre-treatment with NIMOTOP 30 mg tablets. NIMOTOP IV solution and NIMOTOP 30 mg tablets should not be used concomitantly.

NIMOTOP IV is administered as a continuous i.v. 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 with magnesium, dextran 40 solution or HAES® (poly(O-2-hydroxyethyl) starch 6 % in a ratio of about 1:4 (Nimotop:co-infusion). Mannitol, human albumin or blood are suitable for co-infusion.

NIMOTOP solution must not be added to an infusion bag or bottle and must not be mixed with other medications. Administration of NIMOTOP IV 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 central catheter.

SIDE EFFECTS:

Adverse Reactions based on clinical trials with nimodipine:

System Organ Class	Common	Uncommon	Rare

	≥ 1 % to < 10 %	≥ 0,1 % to < 1 %	≥ 0,01 % to < 0,1 %
Blood and lymphatic system disorders		Thrombocytopenia	
Immune system disorders		Allergic reaction Rash	
Nervous system disorders		Headache Hyperkinesia	
Cardiac disorders		Tachycardia	Bradycardia
Vascular disorders	Hypotension Vasodilatation		
Gastrointestinal disorders		Nausea Constipation Diarrhoea Flatulence	Ileus
Hepato-biliary disorders			Transient increase in liver enzymes
General disorders and administration site conditions			Injection and infusion site reactions Infusion site thrombophlebitis

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Since no specific antidote is known treatment must be symptomatic and supportive.

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 30 mg tablets or NIMOTOP IV solution 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, resusitative measure may need to be taken. As no specific antidote is known, subsequent treatment for other side-effects should be aimed at the most prominent symptoms.

IDENTIFICATION:

NIMOTOP 30 mg tablets: Round, butter-yellow, coated tablets with SK on the upper side and the Bayer cross on the lower side.

NIMOTOP IV solution: Clear, slightly yellowish solution.
Parenteral drug products should be inspected visually for particulate matter and colour change prior to administration. Any residual solution should not be kept for later use.

PRESENTATION:

NIMOTOP 30 mg tablets: Blister strips of 10 tablets. 100 tablets contained per box.

NIMOTOP IV solution: 50 ml infusion solution contained in an amber coloured glass vial.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.
Keep the product (blister strips or glass vial) in the original carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

NIMOTOP 30 mg tablets: T/7.1/229
NIMOTOP IV solution: T/7.1/230

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

Bayer (Pty) Ltd
Reg. No.: 1968/11192/07
27 Wrench Road
ISANDO
1609

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

19 April 2013