# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Nimotop 0.02% w/v Concentrate for Solution for Infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 ml vial contains 10 mg of nimodipine (0.2 mg/ml).

Excipients with known effect:
Each 50 ml vial also contains 10 g of ethanol (0.2 g/ml) and 23 mg of sodium (as sodium citrate dihydrate). Please see section 4.4 for further information.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)
A clear, yellow solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Nimotop solution is indicated for the treatment of ischaemic neurological deficits following aneurysmal subarachnoid haemorrhage.

### 4.2 Posology and method of administration

Posology

*Recommended dose - aneurysmal subarachnoid haemorrhage:*

For the first two hours of treatment, 1 mg of nimodipine, i.e. 5 ml Nimotop solution (about 15 micrograms/kg bw/h), should be infused each hour via a central catheter. If it is well tolerated, the dose should be increased after two hours to 2 mg nimodipine, i.e. 10 ml Nimotop solution per hour (about 30 micrograms/kg bw/h), providing no severe decrease in blood pressure is observed.

Patients of body weight 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 solution, or less if necessary).

*Aneurysmal subarachnoid haemorrhage*

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. This should continue for at least five days up to a maximum of 10-14 days.

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 about a further 7 days.

If cerebral ischaemia occurs during prophylactic administration, tablet treatment may be continued to complete the 21-day treatment period or substituted by Nimotop solution (dosage as above). Nimotop solution may be used with or without pre-treatment with Nimotop tablets. In the event of Nimotop tablets and Nimotop solution being administered sequentially, the total duration of treatment should not exceed 21 days. Nimotop solution should not be administered for longer than 14 days. Nimotop solution and tablets should not be used concomitantly.

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 60 mg nimodipine 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.

Paediatric population
Safety and efficacy of nimodipine in patients under 18 years of age have not been established.

Method of administration

Nimotop is administered as a continuous I.V. infusion via a central catheter using an infusion pump. It should be connected to a three-way stopcock using the infusion line provided. The three-way stopcock should be used to connect the Nimotop polyethylene tube with the co-infusion line and the central catheter. (The stopcock must allow for concomitant flow of the Nimotop solution and a co-infusion solution.) Nimotop solution must be administered with co-infusion running at a rate of 40 ml/hr of either sodium chloride 0.9%, glucose 5%, Ringer's lactate solution, lactated Ringer's solution with magnesium, dextran 40, HAES® (poly[O-2-hydroxyethyl]) starch 6%, human albumin 5%, blood or mannitol 10% in a ratio of about 1:4 (Nimotop:co-infusion), which is connected to the second port of the three-way stopcock prior to its connection with the central line catheter.

Nimotop must not be mixed with other drugs so it should not be added to an infusion bag or bottle which contains other drugs.

Nimotop solution may be used during anaesthesia, angiography or surgical procedures.

During surgery a freshly prepared dilute solution of nimodipine (1 ml nimodipine infusion solution and 19 ml Ringer's solution) warmed up to blood temperature may be instilled intracisternally.

This dilute solution of nimodipine must be used immediately after preparation.

**4.3 Contraindications**

Nimodipine solution for infusion must not be used in cases of hypersensitivity to nimodipine or to any of the excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**

Nimotop solution should be used with care when cerebral oedema or severely raised intracranial pressure are 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 (generalised cerebral oedema).

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

Decreased drug clearance may occur in cirrhotic patients receiving Nimotop and therefore close monitoring of blood pressure is recommended in these patients.

A transient rise in liver enzymes may occur during intravenous administration; this usually reverts to normal on completion of treatment. The infusion contains 17% macrogol 400; this should be taken into account during treatment.

Renal function can deteriorate if potentially nephrotoxic drugs (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 (see Section 4.5).

Nimotop contains ethanol
A dose of 10 ml of this medicine administered per hour to an adult weighing 70 kg would result in exposure to 28 mg/kg/h of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 4 mg/100 ml. For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.
Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

Because this medicine is usually given slowly by continuous infusion, the effects of alcohol may be reduced.

The ethanol content of Nimotop may be harmful for those suffering from alcoholism or impaired alcohol metabolism and should be taken into account in pregnant or breast-feeding women and younger children. The amount of alcohol in this medicine may alter the effects of other medicines (See Section 4.5).

Nimotop contains sodium
This medicinal product contains 23 mg sodium per 50 ml bottle, equivalent to 1.15 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Nimotop solution reacts with polyvinylchloride (PVC). Polyethylene or polypropylene are the recommended plastic materials to be used during nimodipine infusion. Polyethylene tubes are supplied with Nimotop solution 50 ml vials. The recommendations on materials to be used during nimodipine infusion must be strictly adhered to, with only polyethylene or polypropylene tubes being suitable.

Nimotop should not be used in concentrated form.

**4.5 Interaction with other medicinal products and other forms of interaction**

Nimotop solution should not be administered concomitantly with Nimotop tablets.

Drugs that affect nimodipine:

Nimodipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or induce this enzyme system (e.g. erythromycin, ketoconazole, itraconazole, fluconazole, indinavir, ritonavir and saquinavir) may, therefore, alter the first pass or the clearance of nimodipine. If co-administration of nimodipine and one of these drugs is unavoidable then the patient's blood pressure should be monitored.

*Fluoxetine*
Concomitant administration of nimodipine with the antidepressant fluoxetine, once steady state has been achieved has led to approximately 50% higher plasma nimodipine levels. 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.

Effects of nimodipine on other drugs:

*Blood pressure lowering drugs*
Nimodipine may increase the blood pressure lowering effect of concomitant antihypertensives, such as

- diuretics
- beta-blockers
- ACE inhibitors
- A1-antagonists
- other calcium antagonists
- alpha-adrenergic blocking agents
- PDE5 inhibitors
- alpha-methyldopa

However, if a combination of this type proves unavoidable particularly careful monitoring of the patient is necessary.

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

Renal function can deteriorate if potentially nephrotoxic drugs (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 deterioration is found discontinuation of the treatment should be considered (See Section 4.4).

*Zidovudine*
In a monkey study simultaneous administration of anti-HIV drug zidovudine i.v. and nimodipine bolus i.v. resulted for zidovudine in significantly higher AUC, whereas the distribution volume and clearance were significantly reduced. The clinical relevance of this interaction is unknown, but since the side-effect profile of zidovudine is known to be dose-related, this interaction should be considered in patients receiving nimodipine and zidovudine concomitantly.

Other forms of interaction:

Since nimodipine solution for infusion contains 23.7 vol % ethanol (alcohol), interactions with alcohol-incompatible drugs should be taken into consideration (see Section 4.4).

Concomitant administration of anti-epileptic drugs (phenobarbital, phenytoin or carbamazepine) markedly reduces the bioavailability of orally administered nimodipine.

The simultaneous administration of cimetidine or sodium valproate may lead to an increase in the plasma nimodipine concentration.

The intake of grapefruit juice is not recommended in combination with nimodipine as it can result in increased plasma nimodipine concentrations due to the inhibition of the oxidative metabolism of dihydropyridines.

Interactions shown not to exist

There is no evidence of a potential interaction between nimodipine and haloperidol.

Concomitant administration of oral nimodipine and diazepam, digoxin, glibenclamide, indometacin, ranitidine and warfarin did not reveal any potential for mutual interaction.

**4.6 Fertility, pregnancy and lactation**

Pregnancy:
There are no adequate and well controlled studies in pregnant women. The safety of this medicinal product for use in human pregnancy has not been established.

Experimental animal studies following oral administration are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation, and peri- and post-natal development. Reproductive toxicology studies in animals after oral administration showed no teratogenic effect. Therefore, if nimodipine solution for infusion is to be administered during pregnancy, the benefits and the potential risks must be carefully weighed according to the severity of the clinical picture.

Breast-feeding:
Nimodipine and its metabolites have been shown to appear in human milk at concentrations of the same order of magnitude as corresponding maternal plasma concentrations. Nursing mothers should be advised not to breastfeed when taking this drug.

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. The relevance of this finding in short-term treatment is unknown.

**4.7 Effects on ability to drive and use machines**

In theory, the possibility of the occurrence of the side-effect dizziness and the amount of alcohol in this medicinal product may impair the patient's ability to drive and operate machinery. However, this is unlikely to be of clinical relevance in patients receiving Nimotop Solution.

**4.8 Undesirable effects**

The frequencies of ADRs reported with nimodipine summarized in the tables below are 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as:
very common (≥ 1/10),
common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000),
very rare (< 1/10,000),
not known (cannot be estimated from the available data).

Table 01: ADR

| **System Organ Class (MedDRA)** | **Uncommon** | **Rare** | **Not known** |
|---|---|---|---|
| Blood and the lymphatic system disorders | Thrombocytopenia | | |
| Immune system disorders | Allergic reaction<br>Rash | | |
| Nervous system disorders | Headache | | |
| Cardiac disorders | Tachycardia | Bradycardia | |
| Vascular disorders | Hypotension<br>Vasodilatation | | |
| Gastrointestinal disorders | Nausea | Ileus | |
| Hepatobiliary disorders | | Transient increase in liver enzymes | |
| General disorders and administration site conditions | | Injection and infusion site reactions<br>Infusion site (thrombo-) phlebitis | |
| Respiratory, thoracicand mediastinal disorders | | | Hypoxia |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; Website: www.hpra.ie.

**4.9 Overdose**

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

In the event of acute overdosage, treatment with nimodipine must be discontinued immediately. Emergency measures should be governed by the symptoms. If the substance was ingested orally, gastric lavage with addition of charcoal should be considered as an emergency therapeutic measure. If there is a marked fall in blood pressure, dopamine or noradrenaline can be administered intravenously.
Since no specific antidote is known, subsequent treatment for other side effects should be governed by the most prominent symptoms.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives
ATC code: C08CA06

Nimodipine is a calcium channel blocker of the dihydropyridine group with preferential activity on cerebral vessels. Nimodipine increases cerebral perfusion, particularly in poorly perfused areas, by arterial dilatation, an effect which is proportionately greater in smaller than in larger vessels.

Nimodipine has a predilective cerebral anti-vasoconstrictive and anti-ischaemic 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 region than in healthy regions.

The ischaemic neurological damage in patients with subarachnoid haemorrhage and the mortality rate are significantly reduced by nimodipine.

**5.2 Pharmacokinetic properties**

The intravenous Nimotop solution is 100% available to the tissues as the peripheral venous blood takes the drug to the lungs and heart and from there to all organs.

Absorption
The orally administered active substance nimodipine is practically completely absorbed. The peak plasma concentration and the area under the curve increase proportionally to the dose up to the highest dose under test (90 mg).

Distribution
The distribution volume (Vss, 2 compartment model) for i.v. 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. Nimodipine is 97-99 % bound to plasma proteins.

Biotransformation
Nimodipine is eliminated metabolically via the cytochrome P450 3A4 system. Nimodipine is eliminated as metabolites, 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 negligible residual activity.

Elimination
Effects on liver enzymes by induction or inhibition are unknown. In humans the metabolites are excreted about 50% renally and 30% in the bile. Attributed to the extensive first-pass metabolism (about 85-95 %) the absolute bioavailability is 5-15 %.

Linearity/non-linearity
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 is not relevant for establishing the recommended dosing interval for the medicinal product.

**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. However, several preclinical findings may be of relevance to the prescribing physician. In a chronic repeat dose toxicity study in dogs, doses of 1 and 2.5 mg/kg/day were shown to be tolerated without adverse effect. However, at the higher dose of 6.25 mg/kg/day, significant changes in ECGs were noted due to disturbances in myocardial blood flow, but there was no indication of histopathological damage to the heart. In pregnant rats, doses of 30 mg/kg/day and higher inhibited foetal growth and resulted in reduced foetal weights. At 100 mg/kg/day embryolethality 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.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Ethanol
Macrogol
Sodium citrate
Citric acid
Water for injections

**6.2 Incompatibilities**

Nimotop solution reacts with polyvinylchloride (PVC). Polyethylene or polypropylene are the recommended plastic materials to be used during nimodipine infusion. Polyethylene tubes are supplied with Nimotop solution 50 ml vials. The recommendation on materials to be used during nimodipine infusion must be strictly adhered to, with only polyethylene or polypropylene tubes being suitable. Nimotop must not be mixed with other drugs so it should not be added to an infusion bag or bottle which contains other drugs.

**6.3 Shelf life**

Unopened: 4 years.
After opening the product should be diluted and administration of the product should start immediately.

**6.4 Special precautions for storage**

Do not store above 25°C. Keep the vial in the outer carton to protect from light.

**6.5 Nature and contents of container**

Light-protective container in cardboard outer containing a 50 ml brown glass Type II infusion vial with grey chlorobutyl stopper laminated with fluoropolymer and a polyethylene infusion line.

The 50 ml bottle is available in packs of 1 bottle and in multi-packs containing 5 bottles (5 packs of 1 bottle).
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

The solution should not be allowed to come into contact with PVC. The only plastic materials suitable for use are polyethylene or polypropylene. Nimotop solution is compatible with glass infusion bottles and infusion packs made of polyethylene, *e.g.,* Polyfusor, Boots.
The solution when in the syringe must be protected from direct sunlight during administration, but is stable in diffuse daylight and artificial light for up to 10 hours.

For single use only. Discard any unused portion.

Nimotop solution should be infused using a glass or rigid plastic (polyethylene or polypropylene) syringe and giving set (Gilette Sabre syringe; BD plastipak syringe; Monoject disposable syringe, Sherwood Medical Ltd; Combidyn tubes, Braun; Nitrocassette giving set, Imed Ltd.).
To penetrate the coated injection stoppers correctly, fine acute injection needles (e.g. 21 gauge) 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.

Nimotop solution is incompatible with infusion bags and any giving sets made of PVC, *e.g.,* Viaflex, Travenol; Steriflex, Boots.

**7 MARKETING AUTHORISATION HOLDER**

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170 Bureaux De La Colline
St Cloud Cedex
92213
France

**8 MARKETING AUTHORISATION NUMBER**

PA25299/001/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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Date of last renewal: 15 February 2009

**10 DATE OF REVISION OF THE TEXT**

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