# Nimotop® (aSAH)

## 1. NAME OF THE MEDICINAL PRODUCT
Nimotop solution for infusion 10 mg (50 mL)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 bottle of Nimotop solution for infusion 10 mg (50 mL) contains 10 mg nimodipine in 50 mL alcoholic solvent.

## 3. PHARMACEUTICAL FORM
Clear slightly yellowish solution

## 4. CLINICAL PARTICULARS
### 4.1 Indication(s)
Prophylaxis and treatment of ischemic neurological deficits caused by cerebral vasospasms following subarachnoid hemorrhage of aneurysmal origin.

### 4.2 Dosage and method of administration
#### 4.2.1 Method of administration
Nimotop solution for infusion 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, lactated Ringer's solution with magnesium, dextran 40 solution or HAES® (poly(O-2-hydroxyethyl) starch 6% in a ratio of about 1:4 (nimodipine: co-infusion). Also mannitol, human albumin or blood are suitable for co-infusion.

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

Nimotop solution for infusion must not be added to an infusion bag or bottle and must not be mixed with other drugs.

Administration of Nimotop solution for infusion should be continued during anesthesia, surgery and angiography.

#### 4.2.2 Dosage regimen
Intravenous infusion:
At the beginning of treatment 1 mg/h nimodipine (= 5 mL Nimotop solution for infusion /h) for 2 h (about 15 µg/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 h to 2 mg/h nimodipine (= 10 mL Nimotop solution for infusion /h) (about 30 µg/kg body weight/h).

Patients whose body weight is appreciably below 70 kg or who have labile blood pressure should be started with a dose of 0.5 mg/h nimodipine (= 2.5 mL Nimotop solution for infusion /h).

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

This dilute solution of Nimotop solution for infusion must be used immediately after preparation.

### 4.2.3 Duration of use

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

If during prophylactic administration of Nimotop solution for infusion, the source of the hemorrhage is treated surgically, intravenous treatment with Nimotop solution for infusion 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.

Therapeutic Use:
If ischemic neurological disturbances caused by vasospasm after aneurysmal subarachnoid hemorrhage 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 solution for infusion, the source of the hemorrhage is treated surgically, intravenous treatment with Nimotop solution for infusion should be continued post-operatively for at least 5 days.

## 4.3 Contraindications

Nimotop solution for infusion must not be used in cases of hypersensitivity to nimodipine or to any of the excipients.

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

This medicinal product 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 "Interaction with other medicinal products and other forms of interaction").

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

### 4.5.1 Drugs that affect nimodipine:

**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.

**Nortryptyline**

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

### 4.5.2 Effects of nimodipine on other drugs

**Blood pressure lowering drugs**

Nimodipine may increase the blood pressure lowering effect of concomitant 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 ionotropic 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 a deterioration is found discontinuation of the treatment should be considered.

**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.

### 4.5.3 Other forms of interaction
Since Nimotop solution for infusion contains 23.7% vol-% of alcohol, interactions with alcohol-incompatible drugs should be taken into consideration (see "Special warnings and precautions for use").

## 4.6 Pregnancy and lactation
### 4.6.1 Pregnancy
There are no adequate and well controlled studies in pregnant women. If nimodipine is to be administered during pregnancy, the benefits and the potential risks must therefore be carefully weighted according to the severity of the clinical picture.

### 4.6.2 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. Nursing mothers are advised not to breastfeed their babies when taking the drug.

### 4.6.3 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.

## 4.7 Effects on ability to drive or use machines
In principle the ability to drive and use machines can be impaired in connection with the possible occurrence of dizziness. In case of using Nimotop solution for infusion, this influence will not be of importance.

## 4.8 Undesirable effects
### 4.8.1 Tabulated list of adverse reactions
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 summarized in the table below. 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).

**Table 01: ADR table**

| System Organ Class (MedDRA) | Uncommon | Rare |
|---|---|---|
| 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 |
| Hepato-biliary disorders | | Transient increase in liver enzymes |
| General disorders and administration site conditions | | Injection and infusion site reactions<br>Infusion site (thrombo-) phlebitis |

## 4.9 Overdose

### 4.9.1 Symptoms of intoxication

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.

### 4.9.2 Treatment of intoxication

In the event of acute overdosage treatment with Nimotop solution for infusion 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

Nimodipine has a predilective cerebral anti-vasoconstrictive and anti-ischemic 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 ischemic neurological damage in patients with subarachnoid hemorrhage and the mortality rate are significantly reduced by nimodipine.

## 5.2 Pharmacokinetic properties

### 5.2.1 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). 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.

### 5.2.2 Protein binding and distribution

Nimodipine is 97 - 99% bound to plasma proteins.

### 5.2.3 Metabolism, elimination and excretion

Nimodipine is eliminated metabolically via the cytochrome P450 3A4 system.

### 5.2.4 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 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

**List of excipients**

**Each 50 mL bottle contains:**

Ethanol 96%, macrogol 400, sodium citrate dihydrate (0.1 g ≅ 1.0 mmol sodium), anhydrous citric acid, water for injection.

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

The active substance of Nimotop solution for infusion is slightly light-sensitive such that 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 h if Nimotop solution for infusion is being given in diffuse daylight or in artificial light.

**Nature and contents of container**
50ml Nimotop infusion solution with 10mg nimodipine. Box of 1 bottle.

**Special precautions for storage**
None, if the bottle remains in the carton.
Protect from direct sunlight, if the bottle is removed from the carton.

**Instructions for use / handling**
Parenteral drug products should be inspected visually for particulate matter and color change prior to administration. Any residual solution should not be kept for later use.

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