Nimotop® (aSAH)

Active ingredient: nimodipine
Infusion solution

COMPOSITION
1 bottle of Nimotop solution for infusion 10 mg (50 mL) contains 10 mg nimodipine in 50 mL alcoholic solvent.
Excipients: ethanol 96 %, macrogol 400, sodium citrate dihydrate (0.1 g ≅ 1.0 mmol sodium) , anhydrous citric acid, water for injection.

PHARMACEUTICAL FORM
Clear intravenous solution for infusion

PHARMACODYNAMICS PROPERTIES

ATC code: C08 CA06
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.

PHARMACOKINETIC PROPERTIES

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.

Protein binding and distribution
Nimodipine is 97 - 99 % bound to plasma proteins.

Metabolism, elimination and excretion
Nimodipine is eliminated metabolically via the cytochrome P450 3A4 system.

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

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.

INDICATION(S)

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

POSOLOGY AND METHOD OF ADMINISTRATION

Unless otherwise prescribed, the following dosage is recommended:

Dosage:
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 instillation:
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.

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 (NIMOTOP:co-infusion). Also mannitol, human albumin or blood are suitable for co-infusion.

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 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.

Duration of use

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 subarachnoid haemorrhage.

If during prophylactic administration of Nimotop solution for infusion, the source of the haemorrhage 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 a day at 4 h 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 60 mg nimodipine/day at 4 h intervals for 7 days is recommended.

If during therapeutic administration of Nimotop solution for infusion, the source of the haemorrhage is treated surgically, i.v. treatment with Nimotop solution for infusion should be continued postoperatively for at least 5 days.

CONTRAINDICATIONS

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

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 minor 100 mm Hg). A marked decrease in blood pressure, particularly where the initial values are elevated, flush, sweating, sensation of warmth of heart, reduction in heart rate (bradycardia) or more rarely an increase (tachycardia).

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*

“Interactions with other medicinal products and other forms of interactions”).

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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.

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.

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”).

PREGNANCY AND LACTATION

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.

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.

Fertility
In single cases of in-vitro fertilization, calcium antagonists have been associated with reversible bio-chemical changes in the spermatozoa's head section that may result in impaired sperm function.

UNDESIRABLE EFFECTS

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 ADR 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)

System Organ Class (MedDRA)	Uncommon	Rare
Blood and the lymphatic system disorders	Thrombocytopenia	
Immune system disorders	Allergic reactions Rash	
Nervous system disorders	Headache	
Cardiac disorders	Tachycardia	Bradycardia
Vascular disorders	Hypotension Vasodilatation	
Gastrointestinal disorders	Nausea	Ileus
Hepato-biliary disorders		Transient increase in liver enzymes
General disorders and administration site conditions		Injection and infusion site reactions Infusion site (thrombo-)phlebitis

Keep the doctor informed of the undesired effects which occur during the use of medication.

EFFECTS ON ABILITY TO DRIVE AND 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 infusion solution, this influence will not be of importance.

OVERDOSE

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.

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.

PHARMACEUTICAL PARTICULARS

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.

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.
Read the package insert carefully. Ask your doctor for more information.
Keep drug out of reach of children!
Specification of finished products: Manufacturer's specification.

Presentation
50 mL Nimotop infusion solution with 10 mg nimodipine. Box of 1 bottle.

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Manufactured by:
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

Or

Solupharm Pharmazeutische Erzeugnisse GmbH
Industriestr. 3
34212 Melsungen
Germany

If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

SafeTrack