SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nimotop 0.02% Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

A sterile solution containing 10 mg nimodipine in 50 ml vials of aqueous alcoholic solvent (0.02%).

Excipients with known effect: ethanol and sodium citrate

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Clear yellow sterile solution for intravenous use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nimodipine 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 µg/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 µg/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.

Duration of treatment

Aneurysmal subarachnoid haemorrhage

Intravenous treatment should begin as early as possible after neurological deficit occurs due to arterial spasm, post subarachnoid haemorrhage. This should continue for at least five days up to a maximum of 14 days.

In the event of surgical intervention during treatment, administration of nimodipine should be continued (dose as above) for at least five days.

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.

Traumatic subarachnoid haemorrhage

Not recommended as a positive benefit to risk ratio has not been established (see section 4.4).

Paediatric Population

The safety and efficacy of Nimotop in patients under 18 years of age have not been established.

Method of administration

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

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

4.3 Contraindications

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

Nimodipine should not be administered to patients during or within one month of a myocardial infarction or an episode of unstable angina.

4.4 Special warnings and precautions for use

Nimotop should not be used in patients with traumatic subarachnoid haemorrhage as a positive benefit to risk ratio has not been established and the specific patient groups that might benefit cannot be identified for this indication.

Nimotop solution should 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).

Nimotop solution must be used with caution in hypotensive patients (systolic blood pressure lower than 100 mm Hg).

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

This medicinal product contains 1 mmol (23 mg) sodium per 50 ml bottle or 5.1 mmol (115 mg) sodium per 250 ml bottle, equivalent to 1.15 % or 5.75 %, respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

Patients with known renal disease and/or receiving nephrotoxic drugs should have renal function monitored closely during intravenous treatment with Nimotop solution (see section 4.5).

Nimodipine is metabolised via the cytochrome P450 3A4 system. Drugs which are known inhibitors of the cytochrome P450 3A4 system and, therefore, may lead to increased plasma concentrations of nimodipine are 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 and valproic acid *(*see section 4.5).

Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction in the nimodipine dose should be considered.

Nimotop contains ethanol

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 section 4.5).

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 given slowly by continuous infusion, the effects of alcohol may be reduced.

4.5 Interaction with other medicinal products and other forms of interaction

Nimotop tablets should not be administered concomitantly with Nimotop solution.

Drugs that affect nimodipine

Concurrent twice daily administration of 30mg nimodipine and daily administration of 20mg of the antidepressant fluoxetine to elderly patients resulted in about 50% higher nimodipine plasma levels, a marked reduction in fluoxetine levels, whilst its active metabolite norfluoxetine was not affected.

Concurrent three times daily administration of 30mg nimodipine and three times daily administration of 10mg of the antidepressant nortriptyline to elderly patients resulted in a slight decrease in nimodipine plasma levels with no effect on nortriptyline plasma levels. The daily dose used in patients with subarachnoid haemorrhage is four times the daily dose used in this trial, thus the clinical significance of this interaction in the treatment of aneurysmal subarachnoid haemorrhage (aSAH) is uncertain.

Nimodipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Although no formal interaction studies have been performed to investigate the potential interaction between nimodipine and inhibitors of cytochrome P450 3A4, the potential for drug interaction and increased nimodipine plasma concentrations cannot be excluded. (See section 4.4).

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

- macrolide antibiotics (e.g. erythromycin)
- anti-HIV protease inhibitors (e.g. ritonavir)
- azole anti-mycotics (e.g. ketoconazole)
- nefazodone.

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).

Animal studies have shown that when nimodipine and zidovudine are administered concomitantly, the AUC for zidovudine was increased, and the volume of distribution and clearance rate decreased. 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 Nimotop solution contains 23.7 vol % ethanol (alcohol), patients should be monitored for any possible interactions with alcohol-incompatible drugs (see Section 4.4.

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

A study examining the effects of 90mg nimodipine (in divided doses) on elderly patients receiving haloperidol did not show evidence of potential interactions. It is unclear whether this study is relevant to use in subarachnoid haemorrhage because of the higher dose of nimodipine used.

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. No reproductive toxicology studies following parenteral administration are available. Reproductive toxicology studies in animals after oral administration showed no teratogenic effect, although studies in animals have shown reproductive toxicity (see section 5.3). If Nimotop solution 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.

Breast-feeding

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

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. 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 may impair the patient’s ability to drive or 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).

System Organ Class (MedDRA)	**Uncommon**	**Rare**	**Not known**
Blood and the 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	
Hepato-biliary disorders		Transient increase in liver enzymes	
General disorders and administration site conditions		Injection and infusion site reactions	
		Infusion site (thrombo-) phlebitis	
Respiratory, thoracic and 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms of intoxication

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.

Treatment of intoxication

In the event of acute overdosage, treatment with Nimotop 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. As no specific antidote is known, subsequent treatment for other side effects should be aimed at 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 dihydropyridine calcium channel blocker with particular cerebrovascular effect. Nimodipine increases cerebral perfusion, particularly in poorly perfused areas, by arterial dilatation, an effect which is proportionately greater in smaller than in larger vessels.

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 reduced by up to 75 % 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

After oral ingestion, absorption is rapid. Peak plasma concentrations are observed 30 to 60 minutes following oral administration. Despite high gastrointestinal absorption of nimodipine, the absolute bioavailability is 5 – 15 %, which is attributed to extensive first pass metabolism (about 85 – 95 %).

Distribution

The distribution volume (Vss, 2 compartment model) for i.v. administration is calculated to be 0.9 – 2.3 l/kg body weight. The total (systemic) clearance is 0.8 – 1.6 l/h/kg. Nimodipine is 97 – 99 % bound to plasma proteins.

Biotransformation

The cytochrome P450 3A4 system plays a major role in the metabolic elimination of nimodipine. 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 other 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.

Linearity/non-linearity

For oral administration, 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 elimination kinetics are linear. The half-life for nimodipine is between 1.1 and 1.7 hours. The terminal half-life is 5-10 hours, and is not relevant for establishing the recommended dosing interval for the medicinal product.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. However, several preclinical findings may be of relevance to the prescribing physician. In chronic repeat dose toxicity studies 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 fetal growth and resulted in reduced fetal weights. At 100 mg/kg/day embryolethality occurred. No evidence of teratogenicity was observed. In rabbits, equivocal evidence of teratogenicity was seen in one study at doses up to 10 mg/kg/day. In two subsequent studies (one at 30 mg/kg/day), these findings were not reproduced. 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

Nimodipine 0.02% solution contains the following excipients:

Ethanol 96%, Macrogol 400, sodium citrate, citric acid, Water for Injections Ph. Eur.

6.2 Incompatibilities

Nimotop solution reacts with polyvinylchloride (PVC) and should not be allowed to come in contact with PVC. Nimotop solution must not be added to an infusion bag or bottle and must not be mixed with other drugs. Crystallization was observed during co-infusion of Nimotop solution with 2.5% xylite in 0.4% sodium chloride solution (Summafusin), Aminosteril (Fresenius) and Ringer's solution DAB7.

6.3 Shelf life

Shelf life of the product as packaged for sale:

	Shelf life		Pack size
Primary packaging material	A	B	(ml)
Brown glass type II infusion vials	4 years	N/A	50

A = Unopened
B = After reconstitution or when the container is opened for the first time, if appropriate.

6.4 Special precautions for storage

Nimotop solution is light sensitive and therefore should be stored in the manufacturer's light-protective container within the cardboard carton at a temperature not above 25°C.

6.5 Nature and contents of container

Brown glass type II infusion vials containing 50 ml of solution; with grey chlorobutyl stopper laminated with fluoropolymer.

150 cm of colorless transparent polyethylene tubing with conus connector for each vial of 50 ml of Nimotop 0.02% Solution for Infusion.

6.6 Special precautions for disposal

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 it is stable in diffuse daylight and artificial light for up to 10 hours. Nimotop solution should be infused using a glass or rigid plastic (polyethylene or polypropylene) syringe and giving set (Gillette Sabre syringe; BD plastipak syringe; Monoject disposable syringe, Sherwood Medical Ltd; Combidyn tubes, Braun; Nitrocassette giving set, Imed Ltd.). Nimotop solution is incompatible with infusion bags and any giving sets made of PVC (*e.g.*, Viaflex, Travenol; Steriflex, Boots).

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.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 5016/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

15/05/2025