SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nimodipine 0.2 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 0.2 mg of nimodipine.

The 50 ml vial contains 10 mg of nimodipine.

Excipients with known effect:

1 ml of solution contains 200 mg of ethanol (96%).

The 50 ml vial contains 10 g of ethanol (96%).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear, slightly yellow solution with pH between 6.0 and 7.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of neurological deterioration caused by cerebral vasospasm secondary to subarachnoid hemorrhage due to aneurysm rupture.

4 CLINICAL PARTICULARS

4.2 Posology and method of administration

Posology

Intravenous infusion.

Treatment begins with a continuous intravenous infusion of 1 mg/h of nimodipine (5 ml of Nimodipine/hour) during 2 hours (approximately 15 micrograms/kg body weight/h). If it is well tolerated and no severe decrease in blood pressure is observed,

the dose should be increased after two hours to 2 mg/h of nimodipine (10 ml of Nimodipine/hour) (approximately 30 micrograms/kg body weight/h. Patients of body weight less than 70 kg or with unstable blood pressure should be started on a dose of 0.5 mg/h of nimodipine (=2.5 ml of Nimodipine/hour), or less if necessary.

Special population

Hepatic impairment:

It should be administered with caution in patients with mild to moderate hepatic impairment (see section 4.4).

Severe renal impairment (creatinine clearance <20 ml/min.):

It should be administered with caution in patients with severe renal impairment (see section 4.4).

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 nimodipine in patients under 18 years have not been established.

Method of administration

This medicinal product is administered as a continuous intravenous infusion via a central catheter connected to an infusion pump using a three-way stopcock. It should be co-administered with one of the following solutions: glucose 5%, sodium chloride 0.9%, Ringer's lactate solution, lactated Ringer's solution with magnesium or dextran 40, HAES® poly(O-2-hydroxyethyl) starch 6% in a ratio of about 1:4 (nimodipine: co-infusion). Also, mannitol or albumin or human blood are suitable for the simultaneous infusion.

Nimodipine must not be added to an infusion bag or bottle and must not be mixed with other drugs (see section 6.2). The solution must be removed from the vial using a syringe. Then, place the needleless syringe in a syringe infusion pump and connect it with a three-way stop cock using a polyethylene tube. Do not use standard PVC tube (see section 6.2). Connect the three-way stopcock, the co-infusion tube and the central catheter. Nimodipine may be used during anesthesia, surgical procedures and brain angiography.

In patients in whom the administration of an additional volume of fluid is not recommended or may be contraindicated, the solution for infusion can be administered through a central catheter, without a co-infusion.

Duration of treatment

Intravenous treatment of aneurysmal subarachnoid hemorrhage should be started as soon as possible and no later than 4 days after the hemorrhage and should be continued during the period of maximum risk of vasospasm, i.e. for 5-14 days after the subarachnoid hemorrhage.

If during the administration of nimodipine, the origin of the bleeding is treated surgically, the i.v. treatment with nimodipine will be continued in the postoperative period for at least 5 days.

After finishing the infusion, it is recommended to continue with the oral administration of nimodipine, tablets 60 mg every 4 hours (6 x 60 mg of nimodipine daily) for approximately 7 days.

4.3 Contraindications

Hypersensitivity to nimodipine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Caution is required in patients with hypotension (systolic blood pressure lower than 100 mm Hg).

Although treatment with nimodipine has not been shown to be associated with increases in intracranial pressure, it should be used with caution in cases of water content of brain tissue (generalised cerebral edema) or if severely raised intracranial pressure are present.

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

Altered liver function may increase the bioavailability of nimodipine due to reduced metabolic clearance. Therefore, both its pharmacological action and adverse reactions (e.g. lowering of blood pressure) may be more pronounced. In these cases, an appropriate dose adjustment should be made, if considered appropriate, according to the blood pressure and if necessary, treatment suspension should be considered (see sections 4.2).

Renal function may be impaired if nimodipine solution for infusion is administered simultaneously with potentially neurotoxic drugs (e.g. aminoglycosides, cephalosporins, furosemide), as well as in patients who already have impaired renal function. In these cases, renal function should be monitored and if renal impairment occurs, treatment suspension should be considered (see section 4.5).

In patients with severe renal impairment (glomerular filtration rate < 20 ml/min) the need for treatment should be carefully assessed and renal function should be monitored at regular intervals (see section 4.2).

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).

Clinical and electrocardiographic monitoring should be performed if the product is prescribed for patients with advanced heart failure or intracardiac conduction problems.

Excipients with known effect

This medicine contains 24% v/v of ethanol (alcohol), which corresponds to an amount of 200 mg per ml.

Co-administration with medicinal products containing, for example, propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, particularly in young children with lower or immature metabolic capacity (see section 4.5).

Because this medication is given slowly through a continuous infusion, the effects of alcohol may be reduced.

This medicinal product may be harmful for those suffering from alcoholism or impaired alcohol metabolism.

The alcohol content 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 medicinal products (see section 4.5).

The amount of alcohol in this medicinal product may alter the effects on the ability to drive and use machinery

This medicinal product contains less than 23 mg (1 mmol) of sodium per dose; that is to say essentially ‘sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

The simultaneous administration of H2-agonist receptor cimetidine or anticonvulsant sodium valproate increase plasma maximum concentration and bioavailability of nimodipine.

Concomitant administration of nimodipine with fluoxetine raised nimodipine plasma levels to 50%. Fluoxetine exposure was markedly decreased, while its active metabolite, norfluoxetine was not affected.

Concomitant administration of nimodipine and nortriptyline led to a slight decrease in nimodipine exposure with unaffected nortriptyline plasma concentrations.

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 cause an additional decrease in blood pressure and a mutual potentiation of negative inotropic action, which can lead to a decompensation of a previous heart failure.

Renal function can deteriorate if nimodipine solution for infusion is simultaneously administrated with potentially nephrotoxic drugs (e.g. aminoglycosides, cephalosporins, furosemide) 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).

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.

Since Nimodipine contains 24% v/v alcohol (200 mg/ml) attention should be paid to possible interactions with drugs that are incompatible with alcohol (see section 4.4).

4.6 Fertility, 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 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

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 nimodipine solution for infusion.

4.8 Undesirable effects

The adverse reactions based in clinical trials with nimodipine in the indication of subarachnoid hemorrhage of aneurysmal origin and 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:

System Organ Class (MedDRA)	**Uncommon (≥ 1/1,000 to <1/100)**	**Rare (≥ 1/10,000 to <1/1,000)**	**Not Known (cannot be estimated from available data)**
Blood and lymphatic system disorders	Thrombocytopenia		
Immune system disorders	Allergic reaction Rash		
Nervous system disorders	Headache		
Cardiac disorders	Tachycardia	Bradycardia	
Respiratory, thoracic and mediastinal disorders			Hypoxia
Vascular disorders	Hypotension Vasodilatation		
Gastrointestinal disorders	Nausea	Ileus	
Hepatobiliary disorders		Transient increase in liver enzymes	
General disorders and administration site conditions		Injection and infusion site reactions Infusion site (thrombo-) phlebitis	

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose

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 overdose

In the event of acute overdosage, treatment with nimodipine must be discontinued immediately. If there is a marked fall in blood pressure, dopamine or noradrenaline can be administered intravenously. Emergency measures should be governed by the symptoms. If the substance was ingested orally, gastric lavage with the addition of activated charcoal should be considered as an emergency therapeutic measure.

Since 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. Dihydropyridine derivatives, ATC Code: C08CA06.

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), by blood or 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. The increase in perfusion is as a rule greater in previously damaged or underperfused brain regions than in healthy regions.

Nimodipine significantly decreases ischemic neurological injury in patients with vasospasm secondary to subarachnoid hemorrhage, improves clinical symptoms and decreases mortality.

Pharmacological studies have confirmed the existence of dihydropyridine-sensitive calcium channels in neurons and have provided additional evidence for the direct neuronal effects of nimodipine.

Nimodipine blocks slow L-type voltage-dependent calcium channels, and as a consequence protects the neuron from the calcium overload observed in ischemic situations and in neuronal degenerative processes.

5.2 Pharmacokinetic properties

Attributed to the extensive first-pass metabolism (about 85 – 95 %) the absolute bioavailability is 5 – 15 %.
With continuous infusions of 0.03 mg/kg/h, average plasma concentrations are reached in a stationary state of 17.6 - 26.6 ng/ml. After intravenous bolus injections,

nimodipine plasma concentrations decrease in a biphasic way with half-lives of 5 – 10 min and approx. 60 min.
It is calculated that for i.v. administration, the distribution volume (VSS, bicompartmental model) is 0.9 - 1.6 L/kg body weight. Total (systemic) clearance is 0.6 - 1.9 L/h/kg.

Nimodipine is 97 – 99 % bound to plasma proteins. In animal experiments, the radioactivity of [14C]-nimodipine crossed the placental barrier. It is likely that a similar distribution occurs in humans, although experimental evidence in this regard is lacking. It has been shown in rats that nimodipine and/or its metabolites appear in breast milk at a much higher concentration than in mother's plasma. The original drug concentrations determined in human milk were quantitatively similar to the corresponding maternal plasma concentrations.

After oral and i.v. administration, nimodipine can be detected in cerebrospinal fluid (CSF) at concentrations of about 0.5% of measured plasma concentrations. This corresponds approximately to the concentration of the free fraction in plasma. Nimodipine is eliminated metabolically via the cytochrome P450 3A4 system, 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.

Effects on liver enzymes by induction or inhibition are unknown. In humans the metabolites are excreted about 50% renally and 30% in the bile.

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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

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, 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 (96 %)

Macrogol 400

Citric acid anhydrous

Sodium citrate

Water for injection

6.2 Incompatibilities

Nimodipine, the active substance, is absorbed by polyvinylchloride (PVC) so only polyethylene (PE) infusion tubing can be used.

Nimodipine must not be added to an infusion bag or vial and must not be mixed with other drugs.

Since Nimodipine contains a percentage in volume of alcohol of 24% (200 mg/ml), attention should be paid to possible interactions with drugs that are incompatible with alcohol.

Also see section **6.6. Special precautions for disposal and other handling.**

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

50 ml type II amber glass vial with chlorobutyl stopper, laminated with fluoropolymer and flip-off capsule.

6.6 Special precautions for disposal

The nimodipine active ingredient is slightly photosensitive, so its use under direct sunlight will be avoided. If direct exposure to sunlight cannot be avoided during infusion, red, yellow, brown or black glass connection tubes and syringes should be used, or the infusion pump and the tubes should be protected with opaque wrappers. However, no special protective measures are needed for up to 10 hours if this medicine is given with diffused daylight or artificial light.

Parenteral pharmaceutical products require visual inspection prior to administration for particulate matter or color change. The residual solution may not be used at any other time.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 46788/0030

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