Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nimotop 30 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 30mg nimodipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablet).
Yellow, film-coated tablet, about 10 mm in diameter, marked with the Bayer cross on one face and with 'SK' on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nimotop tablets are recommended for the prevention of ischaemic neurological deficits following aneurysmal subarachnoid haemorrhage.

4.2 Posology and method of administration

Aneurysmal subarachnoid haemorrhage

Posology:

Unless otherwise prescribed the following dosage is recommended:

The recommended procedure is administration of Nimotop solution for infusion for 5 to 14 days followed by a total daily dose of 360 mg by taking 2 Nimotop tablets at 4 hourly intervals, i.e. 6 times a day.

Alternatively, prophylactic therapy may be initiated using Nimotop tablets. The recommended total daily dose is 360 mg by taking 2 Nimotop tablets at 4 hourly intervals, i.e. 6 times a day.

In patients who develop adverse reactions the dose should be reduced as necessary or the treatment discontinued.

Upon co-administration with cytochrome P450 3A4 inhibitors or inducers, a dose adaption may be necessary (see sections 4.4 and 4.5).

Method of administration:

Administration of Nimotop tablets is recommended for about 7 days following the end of the 5 to 14 days intravenous therapy with Nimotop solution for infusion.

Alternatively, prophylactic therapy may be initiated using Nimotop tablets.

In general, the tablets should be swallowed whole with a little liquid, with or without meals. Grapefruit juice is to be avoided (see section 4.5).

The interval between successive doses must not be less than 4 hours.

Duration of use:

Prophylactic Use

Following the end of the intravenous therapy, it is advisable to continue with oral administration of 6 x 2 Nimotop tablets at 4 hourly intervals (total daily dose 360 mg) for about a further 7 days.

Alternatively, prophylactic administration may be initiated using Nimotop tablets, dosage as above. Administration should commence within 4 days of the onset of subarachnoid haemorrhage and should be continued for 21 days.

Therapeutic Use
After intravenous application, oral administration of 6 x 2 Nimotop tablets at 4 hourly intervals (total daily dose 360 mg) for 7 days is recommended.

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

Special populations
Patients with hepatic impairment
Severely disturbed liver function, particularly liver cirrhosis, may result in an increased bioavailability of nimodipine due to a decreased first-pass capacity and a reduced metabolic clearance. The effects and side-effects, e.g. reduction in blood pressure, may be more pronounced in these patients.
In such cases the dose should be reduced (depending on the blood pressure) or, if necessary, discontinuation of the treatment should be considered.

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

4.3 Contraindications

Nimodipine must not be used in case of hypersensitivity to the active substance or any of the excipients.

The use of nimodipine in combination with rifampicin is contraindicated as the efficacy of nimodipine could be significantly reduced when concomitantly administered. (See section 4.5 Interaction with other medicinal products and other forms of interaction).

The concomitant use of oral nimodipine and the antiepileptic drugs, phenobarbital, phenytoin or carbamazepine is contraindicated as the efficacy of nimodipine could be significantly reduced (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Nimotop tablets 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).

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

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).

Nimodipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or induce this enzyme system may, therefore, alter the first pass or the clearance of nimodipine (see section 4.5 Interaction with other medicinal products and other forms of interaction and Section 4.2 Posology and method of administration / Patients with hepatic impairment).

Drugs which are known inhibitors of the cytochrome P450 3A4 system and, therefore, may lead to increased plasma concentrations of nimodipine are, e.g.:

- 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,
- valproic acid.

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

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:

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 may, therefore, alter the first pass or the clearance of nimodipine (see section 4.2 Posology and method of administration / Patients with hepatic impairment).

The extent as well as the duration of interactions should be taken into account when administering nimodipine together with the following drugs:

Rifampicin
From experience with other calcium antagonists it has to be expected that rifampicin accelerates the metabolism of nimodipine due to enzyme induction. Thus efficacy of nimodipine could be significantly reduced when concomitantly administered with rifampicin. The use of nimodipine in combination with rifampicin is, therefore, contraindicated. (See section 4.3 contraindications).

Cytochrome P450 3A4 system inducing antiepileptic drugs such as, phenobarbital, phenytoin or carbamazepine:
Previous chronic administration of these drugs markedly reduces the bioavailability of orally administered nimodipine. Therefore, the concomitant use of oral nimodipine and these antiepileptic drugs is contraindicated. (See section 4.3 contraindications).

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 Posology and method of administration):

Macrolide antibiotics (e.g. erythromycin)
No interaction studies have been carried out between nimodipine and macrolide antibiotics. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 system and the potential for drug interaction cannot be ruled out at this stage. Therefore, macrolide antibiotics should not be used in combination with nimodipine (see section 4.4 Special warnings and precautions for use).

Azithromycin, although structurally related to the class of macrolide antibiotics, is void of CYP3A4 inhibition.

Anti-HIV protease inhibitors (e.g. ritonavir)
No formal studies have been performed to investigate the potential interaction between nimodipine and anti-HIV protease inhibitors. Drugs of this class have been reported to be potent inhibitors of the cytochrome P450 3A4 system. Therefore, the potential for a marked and clinically relevant increase in nimodipine plasma concentrations upon co-administration with these protease inhibitors cannot be excluded. (See section 4.4 Special warnings and precautions for use).

Azole anti-mycotics (e.g. ketoconazole)
A formal interaction study investigating the potential interaction between nimodipine and ketoconazole has not been performed. Azole anti-mycotics are known to inhibit the cytochrome P450 3A4 system and various interactions have been reported for other dihydropyridine calcium antagonists. Therefore, when administered together with oral nimodipine, a substantial increase in systemic bioavailability of nimodipine due to a decreased first pass metabolism cannot be excluded. (See section 4.4 Special warnings and precautions for use).

Nefazodone
No formal studies have been performed to investigate the potential interaction between nimodipine and nefazodone. This antidepressant drug has been reported to be a potent inhibitor of the cytochrome P450 3A4 system. Therefore, the potential for an increase in nimodipine plasma concentrations upon co-administration with nefazodone cannot be excluded. (See section 4.4 Special warnings and precautions for use).

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 (See section 4.4 Special warnings and precautions for use).

Quinupristin/dalfopristin
Based on experience with the calcium-antagonist, nifedipine, co-administration of quinupristin/dalfopristin may lead to increased plasma concentrations of nimodipine (See section 4.4 Special warnings and precautions for use).

Cimetidine
The simultaneous administration of the H2-antagonist cimetidine can lead to an increase in the plasma nimodipine concentration (See section 4.4 Special warnings and precautions for use).

Valproic acid
The simultaneous administration of the anticonvulsant Valproic acid can lead to an increase in the plasma nimodipine concentration (See section 4.4 Special warnings and precautions for use).

Further drug interaction:

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.

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.

Drug-food interactions:

Grapefruit juice
Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of dyhydropyridine calcium antagonists together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nimodipine due to a decreased first pass metabolism or reduced clearance.
As a consequence, the blood pressure lowering effect may be increased. After intake of grapefruit juice this effect may last for at least 4 days after the last ingestion of grapefruit juice.
Ingestion of grapefruit / grapefruit juice is therefore to be avoided while taking nimodipine (see Section 4.2 Posology and method for administration).

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. An evaluation of experimental animal studies following oral administration does not indicate direct or indirect harmful effects with regard to reproduction, development of the embryo or foetus, the course of gestation, and peri- and post-natal development. If nimodipine is to be administered during pregnancy, the benefits and potential risks must be carefully weighed 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 breast-feed 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 dizziness may impair the patient's ability to drive or operate machinery.

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).

Table 01: ADR table aSAH

System Organ Class (MedDRA)	Uncommon	Rare
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
Hepatobiliary disorders		Transient increase in liver enzymes

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@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. 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

ATC-Code: C08 CA06.

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.

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. Nimodipine is 97 – 99 % bound to plasma proteins.

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.

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 %.

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

Tablet core:
Povidone
Microcrystalline cellulose
Maize starch
Crospovidone
Magnesium stearate

Coating:
Hypromellose
Macrogol 4000
Titanium dioxide E171
Iron oxide yellow E172

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Polypropylene/aluminium foil or polyvinyl chloride/polyvinylidene chloride/aluminium foil blister packs contained in cardboard outer, containing 100 x 30mg tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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