SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nimotop 30mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30 mg nimodipine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, round biconvex tablets with “SK” marked on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nimodipine is indicated for the prevention of ischaemic neurological deficits following aneurysmal subarachnoid haemorrhage.

4.2 Posology and method of administration

Posology

Aneurysmal subarachnoid haemorrhage:

Prophylactic administration - Adults

The recommended dose is two tablets at 4-hourly intervals (total daily dose 360 mg) to be taken with water. Prophylactic administration should commence within four days of onset of subarachnoid haemorrhage and should be continued for 21 days.

In the event of surgical intervention, administration of Nimotop tablets should be continued (dosage as above) to complete the 21 days treatment period.

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

Traumatic subarachnoid haemorrhage:

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

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.

Upon co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers a dose adaption may be necessary (see section 4.5).

Elderly
There are no special dosage requirements for use in the elderly.

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

Method of administration

In general, the tablets should be swallowed whole with a little liquid, with or without food. The interval between successive doses must not be less than 4 hours.

Grapefruit juice is to be avoided (see section 4.5).

4.3 Contraindications

Nimodipine must not be administered in case 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.

The use of nimodipine in combination with rifampicin or the antiepileptic drugs, phenobarbital, phenytoin or carbamazepine is contraindicated as the efficacy of Nimotop tablets could be significantly reduced when concomitantly administered. (See section 4.5).

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 tablets should be used with care when cerebral oedema or severely raised intracranial pressure is 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).

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.

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" and section 4.2 – "*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:

- 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.

<u>Drugs that affect nimodipine</u>

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 – "*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:

The concomitant use of oral nimodipine and rifampicin or cytochrome P450 3A4 system-inducing antiepileptic drugs such as phenobarbital, phenytoin or carbamazepine is contraindicated (see section 4.3). The efficacy of Nimotop tablets could be reduced if these drugs are administered concomitantly.

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.

Upon co-administration with the following inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, an adaptation 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

Although no formal interaction studies have been performed to investigate the potential interaction between nimodipine and these drugs the potential for drug interaction and increased nimodipine plasma concentrations cannot be excluded. (See section 4.4).

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

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 (see section 4.4).

The simultaneous administration of nimodipine with the anticonvulsant valproic acid or the H2-antagonist cimetidine can lead to an increase in the plasma concentration of nimodipine (see section 4.4).

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).

Effects of nimodipine on other drugs

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-effects profile of zidovudine is known to be dose-related, this interaction should be considered in patients receiving nimodipine and zidovudine concomitantly.

Other types of interaction

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.

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. As a consequence, the blood pressure lowering effect may be increased. This effect may last for at least 4 days after the last ingestion of grapefruit juice.

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. Reproductive toxicology studies in animals using oral administration showed no teratogenic effect, although studies in animals have shown reproductive toxicity (see section 5.3). 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.

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 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 the side-effect 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)
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	
Hepatobiliary disorders		Transient increase in liver enzymes	
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. 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

Microcrystalline cellulose, maize starch, povidone, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide El71, iron oxide yellow E172.

6.2 Incompatibilities

None known.

6.3 Shelf life

PP/aluminium blister - 5 years

PVC/PVDC/AL blister – 4 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PP/aluminium or PVC/PVDC/Al blister packs contained in cardboard outer, containing 100 x 30mg tablets

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

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92213 Saint-Cloud Cedex

France

8 MARKETING AUTHORISATION NUMBER(S)

PL 50164/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

21/07/2025