SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nimotop IV 10 mg/50 ml solution for infusion

Nimotop 30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nimotop , solution for infusion:
1 bottle with solution for infusion contains 10 mg nimodipine in 50 ml alcohol solvent.

Excipients with known activity:
This medicinal product contains 23,7 Vol.-% Alcohol und 1 mmol (23 mg) sodium per 50-ml bottle alternatively 5,1 mmol (115 mg) sodium per 250 ml (see Section 4.4).

Nimotop , film-coated tablets:
1 film-coated tablet contains 30 mg nimodipine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nimotop solution for infusion:
Solution for infusion
Clear, pale yellowish solution

Nimotop film-coated tablets:
Film-coated tablet
Round, yellow, biconvex film-coated tablets, marked with the “Bayer cross” on one side and with “SK” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nimotop , solution for infusion:
For the prevention and treatment of ischaemic neurological deficits due to cerebral vasospasms following aneurysmal subarachnoid haemorrhage (aSAH).

Nimotop , film-coated tablets:

After prior infusion of Nimotop , solution for infusion, for the prevention and treatment of ischaemic neurological deficits due to cerebral vasospasms following aneurysmal subarachnoid haemorrhage (aSAH).

4.2 Posology and method of administration

Posology

Nimotop , solution for infusion:
At the start of treatment for a duration of 2 hours: 1 mg nimodipine (= 5 ml Nimotop , solution for infusion)/hr. (approximately 15 µg/kg body weight/hr.). If well tolerated, especially in the absence of major decreases in blood pressure, increase the dose after the 2nd hour to 2 mg nimodipine (= 10 ml Nimotop , solution for infusion)/hr. (approximately 30 µg/kg body weight/hr.). In patients weighing considerably less than 70 kg or with unstable blood pressure, treatment should commence at a dosage of 0.5 mg nimodipine (= 2.5 ml Nimotop , solution for infusion)/hr.

Intracisternal instillation:
During surgical procedures, a freshly prepared, diluted Nimotop solution (1 ml Nimotop , solution for infusion and 19 ml Ringer's solution), warmed up to body temperature, can be instilled intracisternally. This diluted Nimotop solution should be used immediately after preparation.

Nimotop , film-coated tablets:
After prior 5- to 14-day infusion of Nimotop , solution for infusion, a daily dose of 6x2 Nimotop film-coated tablets (6x60 mg nimodipine) is recommended.

In patients with undesirable concomitant effects, the dose may have to be reduced or the treatment discontinued.

In concomitant treatment with medicinal products that inhibit or induce the cytochrome P450 3A4 system, a dose adjustment may be required (see section 4.5).

Patients with impaired hepatic function:
In cases of severe hepatic dysfunction, especially liver cirrhosis, the bioavailability of nimodipine may be increased due to a decreased first-pass capacity and reduced metabolic clearance. The effects and undesirable effects, e.g. hypotension, may be more pronounced in these patients.
In such cases, the dose should be reduced or, if necessary, discontinuation of treatment should be considered.

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

Method and duration of administration

Nimotop , solution for infusion:

For patients in whom volume overload is undesirable or contraindicated, the product can be administered via the central venous route through a catheter, without additional administration of a concomitant solution for infusion. Nimotop , solution for infusion is administered as an intravenous continuous infusion in the bypass via a central catheter using an infusion pump. The lines are connected to each other using a three-way stopcock.

Nimotop , solution for infusion must not be mixed with other medicinal products or added to infusion bags or bottles.

Suitable co-infusions are: glucose 5%, physiological saline solution, Ringer's lactate, Ringer's lactate with magnesium, dextran 40 solutions, poly(O-2-hydroxyethyl) starch 6%, human albumin 5% or blood. Based on experimental results, mannitol can also be administered over a period of up to 24 hours as a co-infusion. The ratio of Nimotop , solution for infusion to concomitant solution for infusion should be 1:4.

It is recommended that Nimotop , solution for infusion also continue to be administered during anaesthesia, surgery and angiography.

Prophylactic administration:

Intravenous treatment should start no later than 4 days after haemorrhaging and should be continued during the period of the greatest risk of vasospasm development, i.e. up to 10-14 days after the subarachnoid haemorrhage.

If, during prophylactic Nimotop use, the source of bleeding is treated surgically, intravenous treatment with Nimotop should be continued postoperatively for at least 5 days.

Upon completion of infusion treatment, oral administration of 60 mg nimodipine 6 times daily at 4-hourly intervals is recommended for approximately 7 more days.

Therapeutic administration:

In the event of pre-existing ischaemic neurological disturbances caused by vasospasm after subarachnoid haemorrhage, treatment should commence as early as possible and continue for a minimum of 5 and a maximum of 14 days.

Thereafter, oral administration of 60 mg nimodipine 6 times daily for 7 days at 4-hourly intervals is recommended.

If, during therapeutic Nimotop use, the source of bleeding is treated surgically, intravenous treatment with Nimotop should be continued postoperatively for at least 5 days.

Nimotop , film-coated tablets:
Upon completion of the 5- to 14-day infusion treatment with Nimotop , solution for infusion, the use of Nimotop , film-coated tablets for about 7 days is recommended. In general, the film-coated tablets are taken without chewing, independently of meals and with sufficient liquid (preferably 1 glass of water). The time interval between each dose should be 4 hours as a minimum. Grapefruit juice must be avoided (see section 4.5).

4.3 Contraindications

Nimotop must not be administered in case of hypersensitivity to the active substance or to any of the excipients.

Nimotop , film-coated tablets:
Nimotop , film-coated tablets must not be used together with rifampicin or the antiepileptic agents phenobarbital, phenytoin and carbamazepine, as the efficacy of Nimotop , film-coated tablets can be significantly reduced by these medicines (see section 4.5).

4.4 Special warnings and precautions for use

Although the use of nimodipine is not associated with an increase in intracranial pressure, close monitoring is recommended in such cases or in patients with elevated fluid levels in brain tissue (generalised cerebral oedema).

Caution is indicated in patients with low blood pressure (systolic blood pressure below 100 mm Hg).

In patients with unstable angina pectoris or within the first four weeks post acute myocardial infarction, physicians should weigh up the potential risk (e.g. reduced coronary artery perfusion and myocardial ischaemia) against the benefit (e.g.
improvement in cerebral perfusion).

Nimotop , solution for infusion:
If combination with antihypertensives is necessary, Nimotop , solution for infusion should be used only with particularly careful monitoring (see section 4.5).
Renal function may deteriorate when co-treating with potentially nephrotoxic medicinal products (e.g. aminoglycosides, cephalosporins, furosemide), as well as in patients with impaired renal function. Careful monitoring of renal function is indicated in such cases. If renal function deteriorates, discontinuation of treatment should be considered (see also section 4.5).

The active substance in Nimotop , solution for infusion is photosensitive to a certain extent. Administration in direct sunlight should therefore be avoided. However, when administered in diffuse daylight or artificial light, Nimotop can be used with no special protective measures for up to 10 hours. If longer light exposure cannot be avoided, appropriate precautions must be taken (e.g. protection of the infusion pump and lines with light-proof wrappings, use of tinted infusion lines).

Warning
This medicinal product contains 23.7% by vol. alcohol. If the dosing instructions are complied with, up to 50 g alcohol is delivered with the daily dose (250 ml solution for infusion). Caution should be exercised in patients with alcoholism, impaired alcohol metabolism, during pregnancy and breast-feeding, in children and high-risk groups such as patients with hepatic disease or epilepsy. The effect of other medicinal products may be impaired or enhanced (see section 4.5). Reaction skills may be impaired when driving and using machines.

This medicinal product contains 1 mmol (23 mg) sodium per 50 ml bottle or 5.1 mmol (115 mg) sodium per 250 ml. This should be taken into consideration in patients on a sodium-controlled (low-sodium/low-salt) diet.

Nimotop , film-coated tablets:

Nimodipine is metabolised via the cytochrome P450 3A4 system. Hence, medicinal products known either to inhibit or to induce this enzyme system may alter the firstpass metabolism or the excretion of nimodipine (see sections 4.5 and 4.2 “Patients with impaired hepatic function”).
The plasma levels of nimodipine may, for example, be increased by the following medicinal products, which are known to be inhibitors of the cytochrome P450 3A4 system:
- macrolide antibiotics (e.g. erythromycin)
- HIV protease inhibitors (e.g. ritonavir)
- azole-type antifungals (e.g. ketoconazole)
- the antidepressants nefazodone and fluoxetine
- quinupristin / dalfopristin
- cimetidine
- valproic acid

If Nimotop , film-coated tablets are co-administered with any of these medicinal products, the blood pressure should be monitored and, if necessary, a reduction in the Nimotop dose should be considered.

Paediatric population

The safety and efficacy of Nimotop in children and adolescents under 18 eyras of age has not been proven. As there is insufficient experience to date concerning use in children and adolescents, nimodipine is not yet intended for treatment of this age group.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that influence nimodipine:

Fluoxetine

Concomitant administration of nimodipine and the antidepressant fluoxetine led to approximately 50% higher plasma concentrations of nimodipine at steady state. The plasma fluoxetine level was considerably reduced, whilst the active metabolite norfluoxetine was not affected (see section 4.4).

Nortriptyline

Concomitant administration of nimodipine and nortriptyline led to a slight decrease in nimodipine exposure at steady state, with no change in plasma nortriptyline concentrations.

Nimotop , film-coated tablets:

Nimodipine is metabolised via the cytochrome P450 3A4 system located both in the intestinal mucosa and in the liver. Hence, the concomitant use of medicinal products that induce or inhibit this enzyme system can affect the first-pass metabolism or clearance of orally administered nimodipine.

Both the extent and duration of interactions should be considered when Nimotop filmcoated tablets are to be administered together with the following medicinal products.

- Rifampicin
  Based on experience with other calcium antagonists, rifampicin can be expected to accelerate the metabolic breakdown of nimodipine by enzyme induction and, hence, potentially to reduce significantly the efficacy of nimodipine in concomitant use. The use of nimodipine in combination with rifampicin is therefore contraindicated (see section 4.3).

- Antiepileptics that induce the cytochrome P450 3A4 system, such as phenobarbital, phenytoin, carbamazepine
  The bioavailability of orally administered nimodipine is significantly reduced by previous long-term treatment with the antiepileptics phenobarbital, phenytoin or carbamazepine. Concomitant oral intake

of Nimotop together with these antiepileptics is therefore contraindicated (see section 4.3).

When co-administering nimodipine and the following inhibitors of the cytochrome P450 3A4 system, the blood pressure must be monitored and the nimodipine dose adjusted, if necessary (see section 4.4):

- Macrolide antibiotics (e.g. erythromycin)
  No studies on the interactions between nimodipine and macrolide antibiotics have been performed. Certain macrolide antibiotics are known to inhibit the cytochrome P450 3A4 system. At present, the possibility of a drug interaction cannot be excluded. Macrolide antibiotics should therefore not be co-administered with nimodipine (see section 4.4).
  Azithromycin has no CYP3A4-inhibiting properties despite its structural affiliation with the class of macrolide antibiotics.

- HIV protease inhibitors (e.g. ritonavir)
  No formal studies have been conducted to investigate potential interactions between nimodipine and HIV protease inhibitors. Medicines of this class have been described as potent inhibitors of the cytochrome P450 3A4 system. A potential for a marked and clinically relevant increase in plasma nimodipine concentrations therefore cannot be excluded during concomitant use with these protease inhibitors (see section 4.4).

- Azole-type antifungals (e.g. ketoconazole)
  No formal studies have been conducted to investigate potential interactions between nimodipine and ketoconazole. Azole-type antifungals are known to inhibit the cytochrome P450 3A4 system. Various interactions have been reported for other calcium antagonists of the dihydropyridine type. Hence, a significant increase in the systemic bioavailability of nimodipine, caused by reduced first-pass metabolism, cannot be excluded during concomitant use with oral nimodipine (see section 4.4).

- Nefazodone
  No formal studies have been conducted to determine a potential interaction between nimodipine and nefazodone, but this antidepressant is known to be an effective inhibitor of the cytochrome P450 3A4 system. Hence, an increase in the plasma nimodipine concentration cannot be excluded during co-medication with nefazodone (see section 4.4).

- Quinupristin / dalfopristin

Based on experience with the calcium antagonist nifedipine, increased plasma nimodipine concentrations may occur when nimodipine and quinupristin/dalfopristin are co-administered (see section 4.4).

- Cimetidine
  Concomitant administration of the H2-antagonist cimetidine can lead to an increase in the plasma nimodipine concentration (see section 4.4).

- Valproic acid
  Concomitant administration of the anticonvulsant valproic acid can lead to an increase in the plasma nimodipine concentration (see section 4.4).

Effects of nimodipine on other medicinal products:

Antihypertensive agents

Nimodipine can potentiate the blood pressure-lowering effect of co-administered antihypertensives, e.g.: - diuretics

- β-receptor blockers
- ACE inhibitors
- A1-receptor antagonists
- other calcium antagonists
- α-receptor blockers
- PDE 5 inhibitors
- alpha-methyldopa

However, if combination with any of these medicinal products should prove unavoidable, particularly careful patient monitoring is required.

Zidovudine

In an experimental study on monkeys, concomitant intravenous administration of the HIV agent zidovudine and nimodipine as an IV bolus dose lead to significantly increased plasma zidovudine levels (AUC), whereas the volume of distribution and clearance were significantly reduced.

Nimotop , solution for infusion:

When nimodipine is co-administered intravenously with a β-receptor blocker, there may be mutual potentiation of the negative inotropic effect and even congestive heart failure.

Potentially nephrotoxic medicinal products

Renal function may deteriorate when co-treating with potentially nephrotoxic medicinal products (e.g. aminoglycosides, cephalosporins, furosemide), as well as in patients with impaired renal function. Careful monitoring of renal function is indicated in such cases. If renal function deteriorates, discontinuation of treatment should be considered (see also section 4.4).

Medicinal products incompatible with alcohol

As nimodipine solution for infusion contains 23.7% by vol. alcohol, interactions with medicinal products not compatible with alcohol should be borne in mind (see also section 4.4).

Interactions with food and drink:

Nimotop , film-coated tablets:

The cytochrome P450 3A4 system is inhibited by grapefruit juice.

Upon co-administration of a calcium antagonist of the dihydropyridine type and grapefruit juice, the plasma concentrations of nimodipine will therefore be increased and its duration of action prolonged due to reduced first-pass metabolism or delayed excretion.

As a result, the antihypertensive effect may be enhanced. This effect may persist for at least 4 days after the last ingestion of grapefruit juice.

During nimodipine treatment, consumption of grapefruit or grapefruit juice must therefore be avoided (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no available experience from appropriate and controlled clinical studies with pregnant women. If Nimotop is to be used during pregnancy, the benefit and possible risks must therefore be weighed up according to the severity of the clinical picture.

Breast-feeding

Nimodipine and its metabolites are excreted in human milk at concentrations of a similar magnitude to those found in maternal plasma. Mothers should therefore not breast-feed during treatment.

Fertility

During *in vitro* fertilisation, calcium antagonists have been associated in individual cases with reversible biochemical changes in the sperm head, which might lead to impaired sperm function. It is not known to what extent this finding is significant in short-term treatment.

4.7 Effects on ability to drive and use machines

In principle, Nimotop may impair the ability to drive and use machines in association with the possible onset of dizziness.

This effect is generally without significance with the use of nimodipine solution for infusion.

4.8 Undesirable effects

Below, the undesirable effects observed in clinical studies with nimodipine for the indication aSAH (placebo-controlled studies: nimodipine N=703, placebo N=692; noncontrolled studies: nimodipine N=2496; date: 31/08/2005) are arranged by CIOMS III categories of frequency. Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

The following categories are used for expressing the frequency of undesirable effects:

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)

	Uncommon	**Rare**
Blood and lymphatic system disorders	Thrombocytopenia	
Immune system disorders	Allergic reaction, skin rash	
Nervous system disorders	Headache	
Cardiac disorders	Tachycardia	Bradycardia
	Uncommon	**Rare**
Vascular disorders	Hypotension, vasodilation	
Gastrointestinal disorders	Nausea	Ileus

Hepatobiliary disorders		Transient rise in liver enzyme values

In addition, the following undesirable effects have occurred with Nimotop , solution for infusion:

	Uncommon	**Rare**
General disorders and administration site conditions		Reactions at the injection and infusion site, thrombophlebitis at the infusion site

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 pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

a) Symptoms of intoxication

As a result of an acute overdose, significant hypotension, tachycardia or bradycardia must be expected, as well as gastrointestinal complaints and nausea after oral administration.

b) Treatment of intoxication

In cases of acute overdose, treatment with Nimotop must be discontinued immediately. Emergency measures should be guided by the symptoms. If orally ingested, gastric lavage with medicated charcoal should be considered as an immediate therapeutic measure. If there is a severe decrease in blood pressure, dopamine or noradrenaline should be intravenously administered. As there is no known specific antidote, further treatment should be guided by the predominant symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cerebral agent, calcium channel blocker ATC code: C08CA06

Mechanism of action

Nimodipine is a calcium antagonist of the 1,4 dihydropyridine group. The substance has good penetration of the blood-brain barrier due to its high lipophilicity. In animal experiments, nimodipine binds with high affinity and selectivity to Ca^{2+} channels of the L-type and thereby blocks transmembrane Ca^{2+} influx. In pathological conditions associated with increased influx of Ca^{2+} ions into nerve cells, e.g. in cerebral ischaemia, nimodipine is assumed to improve their stability and functionality. The ischaemic neurological damage and lethality occurring in subarachnoid haemorrhage were thus significantly reduced by nimodipine.

5.2 Pharmacokinetic properties

Absorption

Absorption of the orally administered active substance nimodipine is virtually complete. As early as 10-15 minutes after tablet administration, the unchanged active substance and its early "first-pass" metabolic products can be detected in plasma. After repeated oral administration (3x30 mg daily), mean peak plasma concentrations (C_{max}) of 7.3-43.2 ng/ml, which are attained after 0.6-1.6 hours (t_{max}), are measured in elderly persons. After a single dose of 30 mg or 60 mg, mean peak plasma concentrations of 16±8 ng/ml and 31±12 ng/ml, respectively, are measured in young persons. The peak plasma concentration and the area under the curve (AUC) rise dose-proportionally up to the highest tested dosage of 90 mg.

With continuous infusion of 0.03 mg/kg/h, mean steady-state plasma concentrations of 17.6-26.6 ng/ml are reached. After intravenous bolus injection, there is a biphasic decline in the plasma nimodipine concentrations with half-lives of 5-10 minutes and approximately 60 minutes. The volume of distribution (V_{ss}, calculated using a twocompartment model) with IV administration is calculated to be 0.9-1.6 l/kg BW. Total (systemic) clearance is 0.6-1.9 l/h/kg.

Protein binding and distribution

Nimodipine is 97-99% bound to plasma proteins. Nimodipine has been shown to cross the placenta in animal trials. Although no such human data are available, placental transfer can also be assumed for humans. In trials on rats, significantly higher concentrations of nimodipine and/or its metabolites were detected in the dam milk than in plasma. In the breast milk of humans, nimodipine is measured at concentrations of a similar magnitude to those found in plasma.

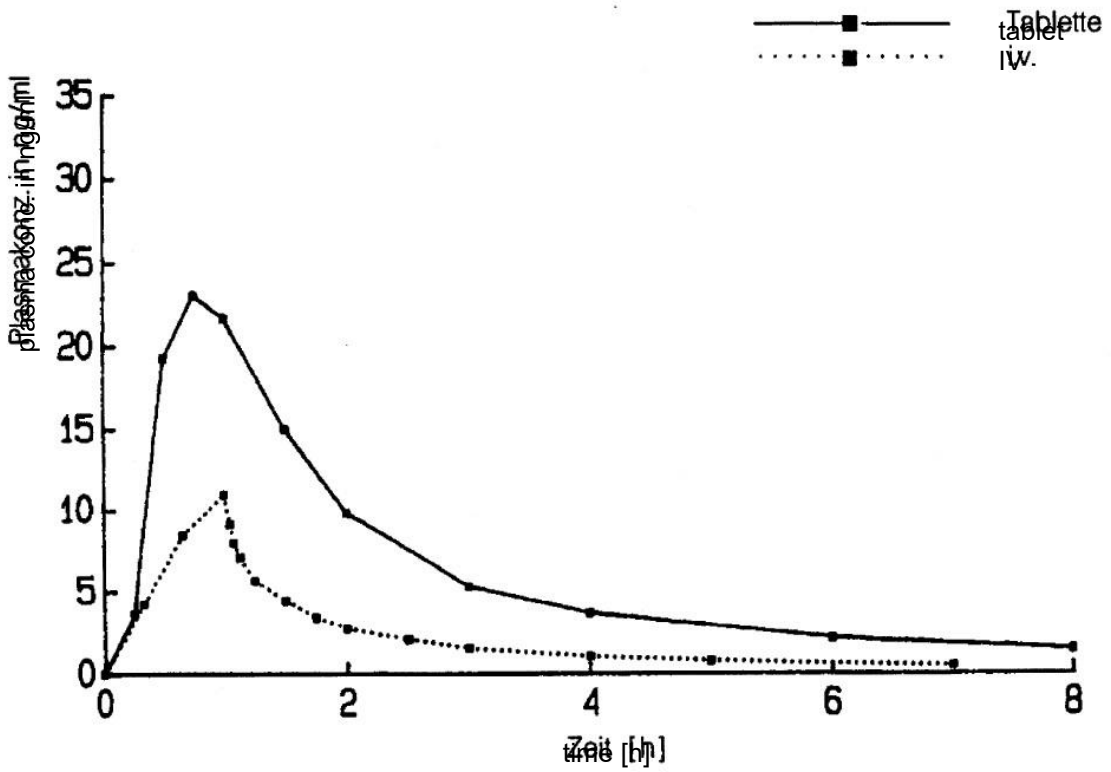
Following oral and IV administration, nimodipine can be detected in the cerebrospinal fluid at concentrations amounting to approximately 0.5% of measured plasma concentrations. These are roughly equivalent to the free concentration in plasma.

Metabolism, elimination and excretion

Nimodipine is metabolically eliminated via the cytochrome P450 3A4 system, primarily by dehydrogenation of the dihydropyridine ring and oxidative ester cleavage. 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 insignificant residual activity.

There are no known effects on liver enzymes by induction or inhibition. In humans, the metabolites are excreted at a rate of about 50% via the renal route and about 30% via the bile.

The elimination kinetics are linear. The half-life of nimodipine is between 1.1-1.7 hours. The terminal half-life of 5-10 hours is not relevant for establishing the dosing interval.



Mean progression of the plasma nimodipine concentrations after oral administration of 30 mg as a tablet and after intravenous infusion of 0.015 mg/kg for one hour (n=24, elderly subjects)

Bioavailability

Due to the high metabolic rate during the first passage through the liver ("first-pass" about 85-95%), the absolute bioavailability is 5-15%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenic potential and effects on male and female fertility.
In pregnant rats, doses of 30 mg/kg/day and higher led to reduced foetal growth and weight. At 100 mg/kg/day, embryolethality occurred. No teratogenic effects were observed. In rabbits, no embryotoxicity or teratogenicity occurred at doses up to 10 mg/kg/day. In one peri-postnatal toxicity study on rats, doses of 10 mg/kg/day and higher caused an increase in mortality and delayed physical development. These findings were not confirmed in other studies performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nimotop , solution for infusion:
Ethanol 96%, macrogol 400, sodium citrate 2 H_2O, citric acid anhydrous, water for injections.

Nimotop , film-coated tablets:
Microcrystalline cellulose, maize starch, povidone K25, crospovidone, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide (E171), iron oxide hydrate (yellow iron oxide, E172).

6.2 Incompatibilities

Nimotop , solution for infusion:
As the active substance in Nimotop , solution for infusion is absorbed by polyvinyl chloride (PVC), only infusion pumps with polyethylene (PE) infusion lines may be used. Nimotop , solution for infusion must not be mixed with other medicinal products or added to infusion bags or bottles.

6.3 Shelf life

Nimotop , solution for infusion:
3 years

Nimotop , solution for infusion is a clear, pale yellowish solution. Bottles with cloudy contents or discolouration are to be excluded from use. Any remaining unused amounts must be discarded.

Nimotop , film-coated tablets:
4 years

6.4 Special precautions for storage

Nimotop , solution for infusion:
Store in the outer carton to protect from light.
For information on protection from light during conditions of use, see section 4.4.

Nimotop , film-coated tablets:
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Nimotop , solution for infusion:
Folding boxes with 50 ml brown glass bottle (glass type 2) with a rubber stopper and coloured crimp cap and infusion line (PE)

Nimotop , film-coated tablets:

Foil 20µm Al sealable to PVC/PVDC

6.6 Special precautions for disposal

N/A

7 MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation holder: Bayer AG 51368 Leverkusen Germany

Manufacturing site address: BAYER AG Kaiser-Wilhelm-Allee 51368 Leverkusen Germany & HAUPT PHARMA MÜNSTER GMBH Schleebrüggenkamp 15 48159 Muenster Germany.

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST / RENEWAL OF THE REGISTRATION

31/03/2026

10. DATE OF REVISION OF THE TEXT

31/03/2026