# Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

# Nimodipine

# Nimotop 30 mg film-coated tablets
# Nimotop 0.2 mg/ml solution for infusion
# Nimotop 4% oral drops

# FI/W/005/pdWS/001

| | |
|---|---|
| **Rapporteur:** | Finland |
| **Finalisation procedure (day 90):** | 14.05.2014 |

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**ADMINISTRATIVE INFORMATION**

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|---|---|
| Invented name of the medicinal product(s): | See section VI |
| INN (or common name) of the active substance(s): | Nimodipine |
| MAH (s): | See section VI |
| Pharmaco-therapeutic group (ATC Code): | C08CA06 |
| Pharmaceutical form(s) and strength(s): | 30 mg film-coated tablet;<br>0.2 mg/ml solution for infusion;<br>oral drops 4% |

# I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in section 4.2 of the SmPC and the corresponding section of PL.

**Summary of outcome**

☐ No change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: section 4.2 of the SmPC

☐ New indication: <section(s) xxxx, xxxx>

# II. RECOMMENDATION

The efficacy and safety of nimodipine in patients under 18 years of age have not been adequately investigated. This information should be included in the product information, as proposed by the MAH:

> ***Dosage and method of administration – Special populations:***
> *Safety and efficacy of nimodipine in patients under 18 years of age have not been established.*

No further action is required.

# III. INTRODUCTION

The MAH of Nimotop and related trade names (see Section VI) submitted the available paediatric data for nimodipine, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. A short critical expert overview has also been provided.

The submitted data consist of six clinical studies performed and reported by Bayer in (mainly) adult patients but which also included a few paediatric patients, and of a literature search. A large portion of the data was related to non-approved therapeutic indications.

The MAH stated that the efficacy and safety of nimodipine in patients under 18 years of age have not been adequately investigated. The MAH proposed the following regulatory action:
To include further information on patients under 18 years of age into the product information:

***Dosage and method of administration – Special populations:***
*Safety and efficacy of Nimodipine in patients under 18 years of age have not been established.*

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

## Product background

### Therapeutic indications

There is no European Product Information for Nimotop and related trade names; there are only purely national marketing authorisations. For the purpose of this paediatric work-sharing assessment, the approved therapeutic indications are limited to treatment of patients with aneurysmal subarachnoid haemorrhage (aSAH).

### Pharmacodynamics

Nimodipine is a calcium channel blocker of the dihydropyridine group with preferential activity on cerebral vessels. According to the SmPC of Nimotop, nimodipine increases cerebral perfusion, particularly in poorly perfused areas, by arterial dilatation, an effect which is proportionately greater in smaller than in larger vessels.

### Pharmacokinetics

Nimodipine is highly lipophilic. After oral ingestion, absorption is rapid and extensive. The absolute bioavailability is only 5 to 15 %, which is attributed to extensive first pass metabolism. The apparent volume of distribution for intravenous administration ($V_{ss}$) is estimated 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. The cytochrome P450 3A4 system plays a major role in the metabolic elimination of nimodipine. The main metabolites have no known pharmacological activity and they are excreted about 50% in the urine and 30% in the bile.

### Dosage in adults

In prevention of ischaemic neurological deficits following aneurysmal subarachnoid haemorrhage the recommended oral nimodipine dose is 60 mg at 4-hourly intervals (total daily dose 360 mg). The recommended intravenous nimodipine dose is 1 mg of nimodipine for the first two hours of treatment (about 15 µg/kg/h). If it is well tolerated, the dose should be increased after two hours to 2 mg nimodipine per hour (about 30 µg/kg/h).

## Condition to be treated - Subarachnoid haemorrhage

The incidence of subarachnoid haemorrhage in most populations is approximately 7-8 per 100 000 person-years but in some populations, e.g. in Finland, the incidence appears to be almost three times higher (1). In children and adolescents SAH is very rare (2-4). Ruptured aneurysm is the most common cause of SAH, approximately in 85% of patients (5). Mortality is almost 50%. Rebleeding is a major cause of mortality and morbidity; endovascular occlusion by coiling or surgical occlusion is performed early in order to prevent rebleeding. Delayed cerebral ischaemia (DCI) is another important cause for mortality and morbidity after aSAH. Peak incidence of DCI is from 5 to 14 days after aSAH. Intravenous and oral nimodipine are used to prevent DCI in patients with aSAH. The length of nimodipine therapy is usually 21 days.

1. Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid hemorrhage: Role of region, year, and rate of computed tomography: A meta-analysis. *Stroke*. 1996 Apr;27(4):625-9.
2. Nilsson OG, Lindgren A, Stahl N, Brandt L, Saveland H. Incidence of intracerebral and subarachnoid haemorrhage in southern sweden. *J Neurol Neurosurg Psychiatry*. 2000 Nov;69(5):601-7.
3. Isaksen J, Egge A, Waterloo K, Romner B, Ingebrigtsen T. Risk factors for aneurysmal subarachnoid haemorrhage: The tromso study. *J Neurol Neurosurg Psychiatry*. 2002 Aug;73(2):185-7.
4. Ostbye T, Levy AR, Mayo NE. Hospitalization and case-fatality rates for subarachnoid hemorrhage in Canada from 1982 through 1991. The Canadian collaborative study group of stroke hospitalizations. *Stroke*. 1997 Apr;28(4):793-8.
5. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet*. 2007 Jan 27;369(9558):306-18.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the clinical studies

Not applicable.

## IV.2 Non-clinical aspects

Not applicable.

## IV.3 Clinical aspects

### 1. Introduction

The MAH submitted summary of results for the following six studies:

- **Study 0159.** Test of the effectiveness and tolerance of nimodipine (BAYE9736) in migraine prophylaxis.
- **Study 0178.** Preliminary presentation of all the cerebral blood flow (CBF) measurements included in the final evaluation with 40, 60 and 80 mg of nimodipine.
- **Study 0479.** A trial of the effect of nimodipine on outcome after head injury. [Bailey I et al. *Acta Neurochirurgica* 1991;110:97-105]
- **Study 500001.** Efficacy and safety of nimodipine in the treatment of traumatic subarachnoid haemorrhage: a multinational, multicentre, double-blind, placebo-controlled study.
- **Report R 3247.** Multinational, multicentre, double-blind, placebo-controlled study in ruptured aneurysms.
- **Report R 4315.** Double-blind study for testing the efficacy and tolerance of two different doses of nimodipine in the prophylaxis of neurological deficits resulting from cerebral vasospasms after subarachnoid haemorrhage.

In each study, almost all study subjects were adults but a few adolescent patients also entered these studies. Importantly, the use of nimodipine in the accepted therapeutic indications was investigated only in two of these studies (R 2347 and R 4325).

### 2. Clinical studies sponsored by the MAH

**Study 0159. Test of the effectiveness and tolerance of nimodipine in migraine prophylaxis.**

This was a single center, open label, planned observation study (pilot study) without a comparison group. The study was conducted in 1980. Study subjects were treated with Nimotop 20 mg tablets TID for 12 weeks. Age over 18 years was one inclusion criteria but one 17-year-old subject was included in the study. Results of the 17-year-old subject were not highlighted in the synopsis.

**Study 0178. Preliminary presentation of all the cerebral blood flow (CBF) measurements included in the final evaluation with 40, 60 and 80 mg of nimodipine.**
This was a single center, single dose, open label study conducted in 1982. A total of 48 subjects who had either survived an ischemic attack (N = 37) or who suffered from cerebral vasospasm (N = 11) were included in the study. Global and regional CBF measurements were carried out using the xenon-133 inhalation method before and 60 minutes after administration of a single oral dose of 40, 60 or 80 mg of nimodipine. Systemic blood pressure and blood gases were also recorded. One patient aged <18 years (17 years of age) participated in the study. Results of the 17-year-old subject were not highlighted in the synopsis.

**Study 0479. A trial of the effect of nimodipine on outcome after head injury.**
[Bailey I et al. *Acta Neurochirurgica* 1991;110:97-105].
This was a randomised, prospective, multicentre, double blind, placebo-controlled parallel group trial to study the effect of nimodipine on the outcome of patients with head injury. The study was supported by Bayer (UK) Ltd. and Bayer (Sverige) AB; the conduct of the study, its statistical analysis and reporting were the responsibilities of the authors, none of whom were employed by Bayer. Age below 16 years was one exclusion criterion; one 14-year subject and one 15-year subject were also included in the study. Treatment (nimodipine i.v. infusion or matching placebo) was started within 24 hours of injury. The initial dose was 1 mg/hour then increased after 2 hours to 2 mg/hour if there were no adverse cardiovascular changes. Treatment was continued for 7 days. The analysis of the effect of treatment was based on 175 patients given placebo and 175 given nimodipine. A favourable outcome (moderate or good recovery) occurred in 53% of patients given nimodipine compared with 49% in the placebo group; this difference was not statistically significant. The exact number of and results for the paediatric patients was not reported by the authors. As the study was conducted and reported by independent researchers, the MAH did not have any other data than the published article.

**Study 500001. Efficacy and safety of nimodipine in the treatment of traumatic subarachnoid haemorrhage: a multinational, multicentre, double-blind, placebo-controlled study.**
This was a 21 day parallel, randomised, double-blind, multicentre study carried out from 1997 to 2000. Subjects were 16 to 70 years old patients with traumatic subarachnoid haemorrhage (tSAH). They were randomised to receive either IV nimodipine or IV placebo treatment, followed by nimodipine oral or placebo oral treatment. 0.5 mg/h nimodipine or matching placebo was administered for the first 2 h to allow assessment of tolerability regarding BP and heart rate. The dose was increased to 1 mg/h for the next 2 h and, if tolerated, to 2 mg/h for 7-10 days. Oral tablets were given for 11-14 days; 60 mg (2x 30 mg) nimodipine or matching placebo, 4-hourly. Medication was down-titrated to 30 mg nimodipine if the subject did not tolerate the full IV dose. The primary objective was to quantify the effect of a 3-weeks treatment with nimodipine on functional outcome, using the Glasgow Outcome Scale (GOS) at 6 months after injury. The total number of subjects enrolled was 592; 591 subjects were valid for safety analysis, 577 subjects for intent to treat analysis (ITT) and 411 subjects were valid for per protocol (PP) analysis. The mean age of the placebo group was 38.2 years (16-70) and of the nimodipine group was 38.7 years (16-71). In the primary ITT analysis, an overall favourable outcome for the endpoint GOS of 73.5% was observed for the placebo treatment group compared to 65.2% for the nimodipine treatment group. For the PP analysis, an overall favourable outcome of 70.4% was observed for the placebo treatment group compared to 64.6% for the nimodipine treatment group. Of the 591

subjects included in the safety analysis, 522 (88.3%) reported 2,797 treatment emergent adverse events (TESS events); 259 (87.5%) in the placebo group and 263 (89.2%) in the nimodipine group. A total of 156 (26.4%) subjects reported 232 drug-related adverse events that occurred with similar frequency in the 2 treatment groups. The duration of diastolic BP <61 mmHg and systolic BP <91 mmHg was higher for nimodipine compared to placebo for the 7 days, but otherwise the safety profiles of the 2 treatment regimens were similar. The number of and results for the adolescent (16 to 17 years of age) study subjects was not highlighted in the synopsis.

**Report R 3247. Multinational, multicentre, double-blind, placebo-controlled study in ruptured aneurysms.**
The study was carried out in 24 neurosurgical centres in North America. Efficacy and safety of nimodipine 30 mg (N = 55) vs. 60 mg (N = 56) vs. 90 mg (N = 59) orally every 4 hours for 21 consecutive days in patients with subarachnoid haemorrhage from a ruptured congenital intracranial aneurysm. Overall, the dose 60 mg every 4 hours appeared to be the most effective and safe of the three doses investigated. The number of and results for the paediatric study subjects was not commented in the summary of results.

**Report R 4315. Double-blind study for testing the efficacy and tolerance of two different doses of nimodipine in the prophylaxis of neurological deficits resulting from cerebral vasospasms after subarachnoid haemorrhage**
This was a multi-center, randomized, double-blind dose-comparison study carried out from May 1985 to September 1987. Nimodipine was administered intravenously as infusion and intracisternally intraoperatively in a dose of 2 mg per hour or 3 mg per hour. The length of treatment was 9 to 14 days for most of the patients. 241 patients between 16 and 76 years of age with SAH of Hunt and Hess Grades I - V were included in the study; 204 of them satisfied the inclusion criteria. Overall, no difference was found between the two treatment groups at the end of treatment or at the follow-up at 6 months after the end of treatment: 77.2 % and 79.6 % of the patients were completely recovered at the end of follow-up. A total of 34 adverse effects were reported in 20 of the 241 patients (8.3 %). 3 adverse effects in the 2 mg/h group and 12 adverse effects in the 3 mg/h group were assumed to be probably or possibly related to nimodipine, primarily decreased BP, bradycardia and increased transaminase level. The number of and results for the adolescent (16 to 17 years of age) study subjects was not commented in the summary of results.

## 3. Discussion and conclusion on clinical studies sponsored by the MAH

Of the six studies above, only studies R 3247 and R 4315 assessed the efficacy and safety of nimodipine in patients with aSAH (i.e. the approved indication); in the other four studies the efficacy and safety of nimodipine in non-approved indications was explored.

It was apparent that only a few adolescent subjects were included in the six clinical studies sponsored by Bayer. The clinical trials sponsored by the MAH provided insufficient data to reliably assess the benefit/risk ratio for the use of nimodipine and recommend the dosage in paediatric patients with aSAH. Therefore, summary of results were considered to be sufficient for assessment.

## 4. Literature review

A literature search was conducted by the MAH in October 2013 in the databases Medline, Embase, Biosis, Current Contents, Derwent Drug File and the company's Product Literature

Database to identify any articles mentioning the use of nimodipine in children or adolescents, regardless of the indication.

A total of 103 published studies or reviews were analysed. 38 publications were considered by the MAH not relevant as they mainly were reviews or regarded as not relevant to the paediatric evaluation. 36 studies were published on approved indications. In regard with the non-approved indications, particular interest has been in the field of migraine and epilepsy. Most of the published studies are dated before the year 2000 with peaks in the decade 1980 and 1990.

According to the MAH's Clinical Overview, about 8 090 patients have been enrolled in the studies relevant for this evaluation. Of those, 296 children were identifiably treated with nimodipine. Most published studies refer to the defined age range (< 18 years), but do not present specific information on this patient subgroup. No single study included in this evaluation has established a safety/risk profile and a specific dose regimen for children. Nimodipine was administered mainly in dosages recommended for adults. The highest reported dose was orally 35 mg/kg every 12 hours, i.e. 70 mg/kg/d. Intravenous dosage ranged from 0.5 – 3 mg/kg/day. Exposure with oral Nimodipine lasted up to 10 months. Some studies exceeded the recommended dosages, thus the safety results are difficult to assess. No critical side-effects, outside of the Company Core Data Sheet were detected.

Published articles with potential relevance for this paediatric assessment are summarized below:

*Treatment of aneurysmal subarachnoid haemorrhage (aSAH)*

**Allen GS et al.** *New Engl J Med* (1983); 308:619-24
125 neurologically normal patients with intracranial aneurysms were enrolled in a multi-institution, prospective, double-blind, randomized, placebo-controlled trial within 96 hours of their subarachnoid haemorrhage, to determine whether treatment with nimodipine would prevent or reduce the severity of ischemic neurologic deficits from arterial spasm. 121 patients met the entry criteria and were analysed. The initial dose was 0.7 mg/kg body weight, thereafter, 0.35 mg/kg was given every 4 hours for 21 days. Age between 15 and 80 years was one inclusion criterion; one or more 17-year-old patient(s) were treated with nimodipine and no patients younger than 18 years of age were treated with placebo. At study day 21, eight of the 60 patients given placebo vs. one of the 56 patients given nimodipine either died or had severe deficits from spasm (P = 0.03; Fisher's exact test). The authors concluded that nimodipine prevented severe deficits from occurring [by preventing arterial spasms], rather than facilitated the recovery of patients with severe deficits. No side effects were reported.

**Auer LM.** *Neurosurgery* (1984); 15:57-66
The author describes a case series of 65 patients operated within 48-72 hours of aSAH and treated with nimodipine for the prevention of symptomatic vasospasm. After the ruptured aneurysm was clipped, a 2.4 x $10^{-5}$ M solution of nimodipine in Ringer's solution was applied locally around the vessels in the operating field for 10 minutes. Immediately thereafter, an i.v. infusion of 0.25 to 0.5 µg/kg/minute was started and continued until day 14 after aSAH, after which 60 mg nimodipine was given p.o. 4 times a day until day 21 after aSAH. The mean age of the patients was 45 years (range, 13 to 80 years). According to the author, no important side-effects such as arterial hypotension or increased intracranial pressure were noted.

**Auer LM et al.** *Acta Neurochir* (1986); 82:7-13
The authors describe a case series of 120 patients operated within 72 hours of aSAH and treated with nimodipine for the prevention of symptomatic vasospasm. After occlusion of the ruptured aneurysm, the exposed arterial segments were rinsed with a solution of a nimodipine in Ringer's solution. I.v. nimodipine infusion at 2 mg/h (approx. 0.5 µg/kg/minute) was started intraoperatively and continued for 7 to 14 days postoperatively. The i.v. treatment was followed by oral administration of nimodipine 240-270 mg per day divided in 4 or 6 doses for another week. Age between 15 and 70 years was one inclusion criterion; two

patients were younger than 20 years (exact age not given). According to the authors, nimodipine was well tolerated and no serious side effects was observed.

**Bazowski P et al.** *Neur Neurochir Pol* (1992); Suppl. 1:25-28 [Article in Polish]
An analysis of certain clinical and laboratory findings of 80 patients (age 11 to 69 years) with ruptured intracranial aneurysms was done. All of them underwent an operation in acute stage. The following prognostic factors were analysed: age of patient, sex, number of previous subarachnoid hemorrhages, clinical status according to the Hunt-Hess scale, CT finding according to Fisher scale, location and number of aneurysms, time of operation, Nimodipine treatment (N=46), body temperature, serum sodium level, white blood count just before operation, mean blood pressure, coexistence of heart and kidney disease. In patients with risk factors, nimodipine improved the outcomes reducing the risk of vasospasm or mitigating its course.

**Bode H and Harders A.** *Eur J Pediatr* (1989); 148:406-411
The authors describe the use of transcranial Doppler sonography in assessing blood flow velocities in the main cerebral arteries. The article includes 11 brief case reports of children with transient stenoses or occlusions. Two children with aSAH were treated with nimodipine: A 9-year-old girl was given intravenous nimodipine 1 mg/h for unspecified time, and a 16-year-old girl was given intravenous nimodipine 2 mg/h for 7 days. Both patients recovered after surgery. The authors also present a case of a 10-year-old boy with astrocytoma surgery who was treated with nimodipine (1.5 mg/h).

**Cedzich C et al.** *J Neurosurg* (1990); 72:806-809
A case report of an 11-month-old boy with an aSAH. Therapy included intravenous nimodipine 0.5 mg/hour in the first 3 days followed by 0.2 mg/hour for the next 7 days. Surgery was performed within the first 72 hours after aSAH. The child recovered without any neurological deficit, hemiparesis, or impairment of verbal ability. No side-effects were reported.

**Cramer SC et al.** *Stroke* (1996); 27:2131-2135
The authors describe the clinical and radiological features of moyamoya syndrome associated with Down syndrome (MM-DS) and explore theories of moyamoya pathogenesis in these patients. The article includes 7 patient cases; in addition, 13 previously reported MM-DS cases are listed in a table. One previous case, a 13-year-old girl with subarachnoid haemorrhage, was treated with intravenous fluids and nimodipine (dosage not given); she recovered uneventfully.
Details of the case are from **Aylett SE.** Pediatr Neurol (1996); 14:259-261.

**Ferro JM et al.** *Acta Medica Portuguesa* (1991); 4:138-140 [Article in Portuguese]
The authors describe a case series of 51 patients with subarachnoidal haemorrhage and compare outcome with a group of patients previously admitted who did not receive nimodipine. Nimodipine was given initially 5 ml/hour [concentration not given] for one hour and 10 ml/hour from the 2$^{nd}$ hour. The mean age of the patients was 46.3 years (range, 12 to 82 years).

**Fusciardi J et al.** *Journées Méditerranéennes d'enseignement postuniversitaire*, 70a, 1986 [Abstract; in French]
The authors describe a case series of 24 patients from 10 to 58 years of age with subarachnoidal haemorrhage anaesthetised with isoflurane. 13 patients had received nimodipine prior to the surgery.

**Gilsbach JM et al.** *Neurosurgery* (1990); 26:458-464
A multicentre, prospective, randomized, double-blind dose-comparison study was conducted to evaluate the efficacy and tolerability of two different doses of intravenous nimodipine: 2 mg/h and 3 mg/h. The infusion was maintained for 9 to 15 days in all patients. In all, 237 patients were enrolled, 204 of whom met the inclusion criteria (e.g. age between 16 and 72 years and surgery within 72 hours after the last aSAH). The youngest subject was 16 years old in 2 mg/h group and 18 years old in 3 mg/h group. The most common causes of death or moderate/severe disability at 6 month follow-up were the initial haemorrhage and consequences of complicated surgery. Delayed neurological dysfunction and related complications were responsible for an unfavourable outcome in only 2 % of the patients. ADRs (probably or possibly related to nimodipine) were reported in 5 patients (5 events) in 2 mg/h group and in 7 patients (12 events) in 3 mg/h group. Overall, bradycardia (N = 5), increased transaminases (N = 4) and hypotension (N = 3) were the most common events observed in the 237 patients.

**Gutknecht J-L et al**. *Agressologie* (1990); 31:340-343 [Article in French]
The authors describe a case series of 88 patients with aneurysmal subarachnoidal haemorrhage treated with tranexamic acid, nimodipine (0.03 mg/kg/h pre- and post-surgery until day 7; from day 8 onwards 60 mg orally, 6 times daily), volume expansion and dopamine. One patient was 5 years old and one was between 15 and 20 years of age.

**Jamjoom A et al.** *British Journal of Clinical Practice* (1993); 47:136-140
This is a retrospective study on 160 consecutive patients who had undergone surgery for aSAH at Frenchay Hospital, England, during 1988 and 1989. One subject was 11 years old and another subject was younger than 20 years of age. Only 117 of the 160 cases (73 %) were treated with nimodipine.

**Kazner E.** (1987) [Article in German]
In einer offenen prospektiven multizentrischen klinischen Studie wurden die Wirksamkeit und Verträglichkeit des Calciumantagonisten Nimodipin (Nimotop®) in der Prophylaxe ischämischer neurologischer Defizite nach einer spontanen Subarachnoidalblutung (SAB) geprüft.
English abstract is not provided. The publication describes 284 patients aged from 17 to 73 years of age.

**König W et al.** In: Advances in Neurosurgery, Vol. 18 [*Stabilizing Craniocervical Operations Calcium Antagonists in SAH Current Legal Issues: Proceedings of the 40th Annual Meeting of the Deutsche Gesellschaft für Neurochirurgie, Würzburg, May 7-10, 1989*; Bushe K-A, Brock M, Klinger M (Eds.)]. Springer-Verlag Berlin Heidelberg 1990.
This is a retrospective study on 108 patients with intracranial ruptured aneurysms admitted to the neurosurgical department in Cologne during the period 1983-1988. Intravenous nimodipine treatment (2 mg/h) was administered to 63 patients for 7-10 days after the SAH and continued by oral medication for a total of 21 days; 45 patients had no nimodipine treatment. The average age of the patients was 46.8 years (range 12 to 73 years).

**Lasner TM et al.** *J Neurosurg* (1997); 87:381-384
The authors performed a prospective analysis of 75 consecutively admitted patients treated for aSAH in order to identify additional risk factors for symptomatic vasospasm. 70 subjects were evaluated, all of whom were treated with nimodipine 60 mg enterally every 4 hours as prophylaxis for cerebral vasospasm. One paediatric subject (age from 10 to 19 years) was included in the study.

**Launay F et al.** *Agressologie* (1990); 31:268-270 [Article in French]
The authors describe a series of 31 patients with intracranial aneurysms treated with endovascular balloon. The focus of the article is to describe the sedation by midazolam and fentanyl and its monitoring. Nimodipine was given as intravenous infusion (1 to 2 mg/hour) or injection into spasmic artery (0.2 mg if needed). Mean age of the patients was 47 years (range from 8 to 77 years).

**Philippon J et al.** *Acta Neurochir* (1986); 82:110-114
A prospective randomised double-blind study was conducted to assess the efficacy of nimodipine in reducing the severity of ischaemic deficits secondary to vasospasm in patients with aSAH. 70 subjects between 15 and 65 years of age were randomised to nimodipine (N = 31; age 44.3 ± 13.2 years; 60 mg orally every four hours for 21 days) or placebo (N = 39; age 45.6 ± 12.8 years). At the end of treatment (Day 21) nimodipine reduced the morbidity caused by vasospasm; effects on overall mortality and morbidity are not clearly stated in the publication. According to the authors, no side effects were noted.

**Raja IA et al.** *Neurol Med Chir Suppl* (1998); 38:134-137
The authors describe the incidence and outcome of operated cerebral artery aneurysms in Pakistan. Data provided by 8 neurosurgical centers from January 1994 to December 1996 were collected. During the period 350 patients presented with SAH, which was caused by ruptured intracranial aneurysm in 240 patients. One patient with aSAH was younger than 11 years of age and 12 patients were between 11 and 20 years of age. The patients were treated with nimodipine to prevent vasospasm but the dose and length of treatment are not presented.

**Schürkämper M et al.** *J Clin Neurosci* (2004); 11:20-24

The authors examined the benefit of dexamethasone in aSAH in a retrospective study. All available patient records with the confirmed diagnosis of an aSAH in the period between January 1994 and June 1999 were evaluated. 295 patients were identified. The median age was 51 years with a standard deviation of 13, the youngest patient was 5 years. 242 patients were treated with dexamethasone, the youngest of these subjects was 14 years. According to the publication, all patients received intravenous nimodipine, usually at a dose of 2 mg/kg, which was changed in uncomplicated cases to oral administration at a dose of 60 mg p.o. q 4 h after one week and then weaned over a period of another week. It is likely that there is a typo and that patients received intravenous nimodipine at a dose of 2 mg/hour.

**Silver P et al.** *Childrens Hospital Quarterly* (1994); 6:237-241
This is a case report of a 9-year-old boy with HIV who had an aSAH. Nimodipine was merely mentioned in the treatment. The patient died of subarachnoid haemorrhage on the 7$^{th}$ hospital day.

**Säveland H et al.** *J Neurosurg* (1992); 76:729-734
The study was conducted to evaluate the overall management results in aneurysmal SAH in Sweden. All patients with verified aSAH admitted between Jun 1, 1989 and May 31, 1990 to the Neurosurgery Departments participating in the study were prospectively included in the study. The participating Neurosurgery Departments covered 81 % of Sweden's 8.59 million inhabitants. A total of 325 patients were admitted. Two patients were younger than 10 years of age and 3 patients were between 11 and 20 years of age. Nimodipine was administered in 269 of the 325 patients (83 %): intravenously in 218, orally in 15, and intravenously followed by orally in 36. Nimodipine dose and length of treatment are not presented.

**Wronski J et al.** *Polski tygodnik lekarski* (1992); 47:442-444. [Article in Polish]
The authors present their own experience in the treatment of 209 patients with aSAH with nimodipine. The patients were from 11 to 73 years old. No information on dosage of nimodipine dose is presented.

**Öhman J and Heiskanen O.** *J Neurosurg* (1989); 70:55-60
The purpose of the study was to identify the optimum time for surgery in patients with ruptured aneurysms in the anterior cerebral circulation who are in good condition (Hunt and Hess Grades I to III). 216 patients aged 16 to 65 years were enrolled in the timing study: operation 0 to 3 days vs. operation 4 to 7 days vs. operation at 8 days or later after the aSAH. Mean (SD) age of the early, intermediate, and late surgery groups was 42.6 (10.4), 45.7 (12.1), and 43.8 (10.2) years, respectively. 159 of the 216 subjects were in addition randomly assigned to nimodipine (N = 79; intravenous infusion 0.5 µg/kg/min for 7-10 days plus 60 mg six times daily for additional 11-14 days) or matching placebo (N = 80). Early surgery was not associated with higher mortality or morbidity rates, and at 3 months after the aSAH there was a trend toward better results at early surgery group. Nimodipine treatment was associated with a significant reduction of delayed ischemic deterioration.

**Öhman J et al.** *J Neurosurg* (1991); 74:8-13
The purpose of the study was to assess the late outcome at 1-3 years after the aSAH and the occurrence of infarcts visualized by CT in good-grade aSAH patients (Hunt and Hess Grades I to III). 213 patients aged 16 to 70 years were randomly assigned to nimodipine (N = 104; intravenous infusion 0.5 µg/kg/min for 7-10 days plus 60 mg six times daily for additional 11-14 days) or matching placebo (N = 109). Mean (SD) age of nimodipine and placebo groups was 44.7 (11.8), and 45.6 (10.7) years, respectively. Overall mortality and morbidity did not significantly differ between the two groups but mortality from delayed ischemic deterioration was more common in placebo group (P = 0.01).

## *Other studies with paediatric patients (off-label indications)*

**Alia G and Mattaliano A.** *La Clinica Terapeutica* (1993); 143:295-301 [Article in Italian; no English abstract]
The information below is based on the Annex of the Clinical Overview.
Open-label (apparently nonrandomised) trial. The authors report on the use of nimodipine in 36 patients for coma due to severe cerebral lesions (20 haemorrhagic, 2 ischaemic, 9 post-anoxic, 4 traumatic, 1 neoplastic). Median age of the patients was 45 years (range 11-69). In addition to resuscitatory therapy,

all patients were given nimodipine per os, 60 mg every 4 hours for 21 days. In all patients, survival, duration of the coma and degree of disability, according G.O.S„ were evaluated and compared with 32 comatose patients suffering from similar diseases, but not treated with nimodipine. Mortality was lower in the patients treated with nimodipine (11.1% vs. 56.2%) as well as disability of surviving patients. Data of the paediatric patient(s) is not available.

**Arellano B et al.** *Acta Otorrinolaring Esp* (1997); 48:513-516 [Article in Spanish]
The information below is based on the Annex of the Clinical Overview.
A retrospective study (case series) of 40 patients with sudden hearing loss, age from 11 to 63 years. Patients were given a combined treatment with steroids, nimodipine, heparin, and oxygen. Patients were divided into two groups by intravenous or oral treatment. Nimodipine dose was 30 mg/8 hours. No specific information on the effect of nimodipine in children.

**Aslan A et al.** *J Neurosurg Sci* (2012); 56:247-253
Antioxidative effect of nimodipine was investigated in patients with severe head trauma in a non-blinded study with two treatment schedules. The patients in group A (N = 5) were treated according to the standard procedures without nimodipine. The patients in group B (N = 5) were treated with standard procedures plus intravenous nimodipine for one week (1 mg/h for the first two hours, and 2 mg/h thereafter). Average age in group B was 39.2 ± 15.4 years; no special reference to children was made.

**Battistella PA et al.** *Headache* (1990); 30:264-268
An 8-month, double-blind, placebo-controlled crossover trial on use of nimodipine in migraine prophylaxis in 7 to 18 years old children and adolescents. After a 4-week medication-free run-in period, 19 subjects (Group 1) received a placebo while 18 (Group 2) received nimodipine (10-20 mg t.i.d., according to body weight), for 12 weeks. After a 4-week wash-out period, the groups switched therapy for a further 12 weeks. 30 patients completed the trial and the number of dropouts was comparable in the 2 groups; dropouts occurred “for reasons unrelated to any side effects”. The only side-effect during nimodipine treatment was mild abdominal discomfort (3 cases).

**Blagodatsky M et al.** *Stereotact Funct Neurosurg* (1997); 67:117.
[Abstract: World Society for Stereotactic and Functional Neurosurgery 12$^{th}$ Meeting, Lyon, July 1997]
The authors present a case series of 19 patients (aged 7-45 years) with spinal cord injury. All patients underwent transplantation of fetal neural tissue; 7 patients received also intravenous nimodipine (5 ml/h for 2 hours followed by 10 ml/h for 7 days). According to the authors, both groups improved but patients in the nimodipine group improved more. No specific information available regarding the paediatric patient(s) in the study.

**Calder K et al.** *Pediatric Emergency Care* (2003); 19:320-328
The authors present 3 cases of paediatric stroke and a review. One patient, a 12-year-old girl with widespread intraventricular haemorrhage caused by arteriovenous malformation, was treated with nimodipine (and dexamethasone and fosphenytoin). No information on dosage is given. The patient was asymptomatic on discharge on day 11.

**Casara GL et al.** *Boll Lega It Epil* (1990); 70/71:137-138 [Article in Italian]
Seven patients aged from 3 to 16 years with symptomatic generalized epilepsy (5 cases) and partial symptomatic epilepsy (2 cases) were studied in an uncontrolled, 8-week, open-label trial; they entered in the study after failure of polytherapy with at least two conventional drugs at maximum tolerated doses. Nimodipine was added on the preceding treatment at doses of 1-1.5 mg/kg/day in three doses. Nimodipine was partially effective in 4 cases. “Relevant side effects” were not observed.

**Castellana M et al.** Calcium entry blockers in the treatment of primary headache in childhood. Our experience with flunarizine and nimodipine. In: *Headache in children and adolescents*. Lanzi G, Balottin U, Cemibori A (Eds.). Elsevier Science Publishers B.V. 1989.
Randomised, open-label, cross-over study. 35 patients between the ages of 8 and 10 years suffering from primary accessional headache were randomised, five of whom were excluded because they did not return to the clinic. The study began with a 30-day run-in period without therapy. Patients were treated with oral nimodipine 10 mg t.i.d. for 30 days and subsequently, after a 30-day wash-out period, with flunarizine 5 mg q.d. for 30 days (Group A) or vice versa (Group B). After the latter treatment period, a 30-day

observation phase took place. There was no placebo group in the study. The number of headache attacks and analgesic consumption decreased significantly (P<0.001) in both groups compared with the run-in phase. 2 cases of moderate flushing were observed with nimodipine.

**Davanzo PA et al.** *J Child Adolesc Psychopharmacol* (1999) ;9:51-61
A case report of nimodipine in the treatment of a 13-year-old boy with refractory, ultradian rapid cycling, bipolar disorder type I. Nimodipine capsules was started at 30 mg at bedtime and titrated up to 60 mg t.i.d. over a period of 12 days. Concomitant medication at discharge included levothyroxine, methylphenidate, and chlorpromazine. 3 years later the patient was still using nimodipine 180 mg daily. Nimodipine serum levels were measured once (54 ng/ml; apparently the peak plasma level at 0.7 hours after ingestion).

**de Falco FA et al.** *Epilepsia* (1992); 33:343-345
Case series. The authors describe 21 epileptic patients with mental retardation with seizures refractory to usual antiepileptic drugs (AEDs, including carbamazepine, phenobarbital, phenytoin, and valproate) who received oral nimodipine 30 mg t.i.d. for 12 weeks as add-on therapy. The study was not controlled. Four paediatric patients (age 11, 13, 14, and 16 years) were included in the study. Overall, no significant changes in serum AED levels or electrolytes were found. One patient showed a decrease in BP.

**Fink JK et al.** *Neurology* (1990); 40 Suppl. 1:362 [Abstract]
Case report. The authors describe a patient with alternating hemiplegia of childhood (AHC); age not specified. The patient was treated with (probably oral) nimodipine 300 mg/day for 4 months.

**Hans P et al.** *Acta Anaesthesiologica Belgica* (1994); 45:175-178
Case report. A 1-year-old 10 kg girl was admitted to hospital after a severe head injury (television fell on her head). Initial treatment included cerebrospinal fluid drainage, surgical removal of extradural haemorrhage, sinus repair, propofol and thiopentone. After the acute phase propofol and thiopentone were discontinued, prophylactic phenytoin (50 mg b.i.d.) was maintained. On the 3$^{rd}$ day she developed hypotonic polyuria with hypernatremia which was treated with desmopressin. On the 6$^{th}$ day she developed generalized seizures; plasma phenytoin level was above the therapeutic range (33 µg/ml). The seizures were temporarily stopped by diazepam and phenobarbital. On the 7$^{th}$ day hyponatremia (123 mMol/l) was observed; seizures recurred and did not respond to phenytoin, phenobarbital and clonazepam. Nimodipine infusion at a rate 0.6 mg/h resulted in complete seizure control in 30 minutes. On the 8$^{th}$ day plasma natrium level was normal (135 mMol/l). Nimodipine infusion was continued for 5 days with phenobarbital. The patient recovered.

**Harders A et al.** Traumatische Subarachnoidalblutung und ihre Behandlung mit Nimodipin. In: *Autorisierte Übersetzung aus: Joumal of Neurosurgery*; Vol. 85/Juli 1996:82-89
[Article in German. No English abstract, no English summary in the Clinical Overview]
Apparently, 123 patients aged 16-70 years were enrolled. Number of children is not given.

**Kulak W and Sobaniec W.** *Neurosciences* (1993); 19:101-106.
Case series. The authors describe 3 children (age 6, 15, and 17 years) for whom nimodipine was added on top of previous AEDs (valproate with or without carbamazepine). Intravenous nimodipine was given at a dose of 1 to 2 mg/h for 72 hours and subsequently orally 60-90 mg/day for 6 months. During the infusion, heart rate increased by 15-23% and BP decreased by 13%. Headache, palpitations, and flushing also appeared. No changes in haematological or biochemical parameters were observed.

**Lee TT et al.** *Pediatr Neurosurg* (1998); 29:300-303
This case report describes a 15-month-old female who developed diffuse cerebral vasospasm after resection of a cerebellopontine angle primitive neuroectodermal tumor. The patient developed an acute dense left hemiparesis 16 days postoperatively. Initial MRI and diffusion study were unremarkable, though a magnetic resonance angiography 1 day later demonstrated severe intracranial vasospasm of both carotid and vertebral arteries. The vasospasm was confirmed with cerebral angiography. The patient progressed to bihemispheric infarcts with laminar necrosis despite combination therapy with anticoagulation, pharmacological hypertension with dobutamine, hypervolemia, and nimodipine (dosage not given). In light of her neurological condition and failure to respond to maximal medical therapy the decision was made to discontinue aggressive medical therapy after 2 weeks. The patient expired.

**Li Y et al.** *Chin J Hosp Pharm* (1997); 17:109-110 [Article in Chinese; no English abstract]
The information below is from the Annex of the Clinical Overview.
Randomised, placebo-controlled prospective study in 95 new-born babies with neonatal hypoxic-ischemic encephalopathy. All the neonates had a clear history of perinatal hypoxia and postnatally they exhibited symptoms and signs of neurological excitation or depression. Brain CT showed intracranial haemorrhage in 41 cases (SAH in 36 cases, cerebral haemorrhage in 2 cases, intraventricular haemorrhage in 2 cases, subdural haemorrhage in 1 case). Study subjects were randomised to nimodipine (N = 55) or placebo (N = 40) on top of standard treatment. Nimodipine was given orally 3-5 mg/kg/day in three doses (total daily dose approximately 30-50 mg) for 10-14 days. From clinical observation and statistical treatment, the nimodipine treatment group was clearly superior to the control group, and the between-group difference in the overall efficacy was highly significant ($\chi^2$ =15.362, P<0.01). There was no difference between the two groups in mild brain injury (P>0.05), but the differences in moderate and severe brain injury were significant (P <0.05 for both). Adverse events were not specified.

**Malashkhia VY et al.** *J Child Neurol* (1996); 11:500-501
Randomised, open-label study in 68 children (age 6.1 ± 3.7 years, range 1 to 14) with complex partial or generalized seizures. Before the trial the patients were treated with phenobarbital, phenytoin, carbamazepine, diazepam, clonazepam, primidone, and valproate, often as polytherapy. All AEDs were tapered so that 1 month before the study all patients were off all AEDs. Four patients were withdrawn at baseline because of a marked increase in seizure frequency. Patients were randomised to receive either phenobarbital 1.0 mg/kg b.i.d. with oral nimodipine 35 mg/kg b.i.d. for 6 months (Group 1, N = 36) or phenobarbital 1.0 mg/kg b.i.d. (Group 2, N = 32). A 50% or greater reduction of seizure frequency was found in 31 patients (86.1%) of Group 1 as compared with 12 patients (37.5%) from Group 2 (P < .001). Mild side effects were noted in patients from Group 1: decreased BP (1 patient, 2.7%), tachycardia (2 patients, 5.4%), diarrhoea (3 patients, 7.1%), and rash (1 patient, 2.7%). Plasma levels of phenobarbital and nimodipine were not measured.

**Pelliccia A et al.** *Developmental Medicine and Child Neurology* (1990); 32: 1114. [Letter]
**Pelliccia A et al.** *Boll Lega It Epil* (1990); 70/71:139 [Article in Italian]
It seems that the same study is published twice.
Case series. The authors describe 20 children (age 3-14 years) with drug-resistant lesional epilepsy who were treated with oral nimodipine (1.5-2 mg/kg/day in three doses) as an additional drug. 5 patients showed signs of hypotension despite slow introduction of nimodipine and the therapy had to be discontinued.

**Pelliccia A et al.** *Boll Lega It Epil* (1993); 82/83:153-154 [Article in Italian]
**Matricardi M et al.** *Epilepsia* (1993); 34 Suppl. 2:124 [Abstract: 20$^{th}$ IEC Proceedings]
It seems that the same study is reported both as a congress abstract and as an article.
A double-blind, placebo-controlled, cross-over trial of nimodipine, as add-on drug was performed on 17 patients (median age 15.5 years, range 5 to 22 years) with drug-resistant symptomatic epilepsy. Treatment periods of 12 weeks (nimodipine 2 mg/kg/day in three doses and matched placebo) were followed by wash-out period of 2 weeks. Three patients withdrew (1 side effects, 2 non-compliance). Modifications in AED blood levels during nimodipine treatment were noted, with significant increase in carbamazepine values and decrease in phenobarbital values.

**Raieli V et al.** (1997) [Abstract: XXX National Congress SIN]
The authors describe two cases (aged 11 and 12 years) of “The Red Ear Syndrome”, characterised by presence of burning, unilateral pain and by change of the ear in the characteristic colour. In one case the therapy with nimodipine achieved a remission of these episodes (dosage not given). No further information is available.

**Ruxiang X et al.** *Journal of Medical Colleges of PLA* (1995); 10:198-201
A total of 488 cases of severe craniocerebral trauma with Glasgow Coma Scale 3-8 score were recruited into the clinical study. The mean age of patients was 38.9 years (range 8 to 67 years). The patients were divided into two groups: (1) therapeutic group (346 cases) treated with nimodipine in addition to conventional therapy; (2) control group 142 cases treated with conventional therapy only. The children received intravenous nimodipine 100-250 µg/kg/day for 10-15 days followed by oral nimodipine for one month. CT scanning showed that in the patients treated with nimodipine, the increase of intracranial

pressure was not very remarkable, and the cerebral oedema alleviated markedly. The rate of good recovery at 3 months in nimodipine and control groups were 80% and 56%, respectively, and mortality rates 18% and 34%, respectively. Detailed information on nimodipine efficacy and safety in children is not available.

**Song Y et al.** *Shanxi Medical Journal* (1998); 27:141-142 [Article in Chinese, no English abstract]
The information below is taken from the Annex of the Clinical Overview.
In order to evaluate the therapeutic and protective value of nimodipine, the effect on paediatric acute cerebral oedema of the calcium channel blocker nimodipine when given at different times after onset was observed and evaluated. 41 children with cerebral oedema are double blind randomized into two groups, 20 patients with nimodipine, 21 without. 8 patients were younger than 1 year, 10 patients 1-3 years, 13 patients 3-6 years, 6 patients 6-9 years, and 4 patients >9 years. The nimodipine group was randomly divided according to the time of drug administration following admission due to disease onset, namely 8 cases who were administered the drug within 24 hours of onset, 6 cases within 48 hours, and 6 cases within 72 hours. After admission to hospital, all the patients were administered with 0.5mg/kg/day to 1mg/kg/day nimodipine, either orally or nasally. Improvement of oedema formation was seen under nimodipine; also the benefit of early onset of treatment with nimodipine was shown. Safety parameters were not reported.

**Volpe E et al.** *Boll Lega It Epil* (1990); 70/71:125-126 [Article in Italian]
**Volpe E et al.** *Giornale di clinica medica & basi razionali della terapia* (1991); 21:153-157 [Article in Italian]
It seems that the same study is published twice.
Case series. The authors describe 25 epileptic patients for whom oral nimodipine was started for 6 months in addition to previous AEDs. Four paediatric patients (age 9, 16, 17, and 17 years) were included in the study; their nimodipine daily dose was 30 to 60 mg. Side effects were observed in 7 of 25 patients (28%) but no patients discontinued the study because of side effects. According to the authors, no significant influences on plasma concentrations of AEDs were observed.

**Wang N et al.** *Anesth Analg* (1997); 84:1160-3
Case report. The authors describe a 9-year-old girl with moyamoya diseas and a large atrial septal defect (ASD). Her history included seizures, asthma, and attention deficit disorder; recent MRI angiography demonstrated supraclinoid bilateral internal carotid artery total occlusion without areas of cerebral infarction. The patient underwent general anaesthesia for attempted device control of the ASD followed by uneventful surgical closure with cardiopulmonary bypass. Prophylactic nimodipine was begun 15 hours prior to surgery (30 mg orally every 4 hours) with close monitoring of arterial BP for possible hypotensive response.

**Zhang P et al.** *Chinese Medical Journal* (1995); 108:420-2
Nimodipine was used in 20 elective neurosurgical patients (mean age 39.5 years, range 14-60 years) to induce controlled hypotension under general anaesthesia during intracranial operation. Sodium pentobarbital and atropine were used for premedication. Anaesthesia was induced with intravenous fentanyl, droperedol, thiopentone, and succinyline, and maintained with inhaled enflurane. Controlled hypotension was induced with intravenous 0.02% nimodipine. The starting infusion rate was 600-800 µg/kg, to reduce the mean arterial pressure (MAP) to 55-60 mmHg. One unit of Innovar was used intravenously in two patients because the blood pressure was not reduced in 5 minutes. The duration of controlled hypotension was 30-60 min and the total nimodipine dose in each patient was 4-12 mg. Systolic BP decreased by 31.6%-35.6%, diastolic BP by 36.1%-41.9%, and MAP by 33.0%-37.7% compared with pre-hypotension values. The heart rate remained stable and there were no changes in ECG and pulmonary parameters.

## 5. Discussion and conclusion on published literature

*Treatment of aneurysmal subarachnoid haemorrhage (aSAH)*
Only few paediatric patients were included in the studies, which is to be expected because aSAH is rare in children less than 18 years of age. The adolescent patients were apparently given the same nimodipine dosage as the adults.

*Other indications*
Most of the published studies explored efficacy and safety of nimodipine as add-on therapy in drug-resistant epilepsy in early 1990's. There are insufficient data to assess the efficacy: The number of subjects in the studies and case series is small, nimodipine dosage was variable, and most studies were non-blinded. The limited data suggest that undesirable effects in paediatric subjects might be similar to those observed in adults. However, it is not known how rigorously the adverse events were monitored in the published studies.

*Conclusion*
It was concluded that the published literature is too limited to reliably assess the benefit/risk and to recommend the dosage of nimodipine in paediatric patients.

### 6. Pharmacovigilance data

Since first registration in 1985 to the data lock point 04-Nov-2013 Global Pharmacovigilance Bayer HealthCare received a total of 15 case reports on nimodipine in paediatric subjects. The MAH concluded that the safety profile of nimodipine in paediatric patients generally appeared to be in line with that of the adult population but because the data are very limited one must be cautious in drawing conclusion.

## V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

It is concluded that the studies sponsored by the MAH and the published literature are too limited to recommend the use and dosage of nimodipine in treatment of aneurysmal subarachnoid haemorrhage in paediatric patients.

- **Recommendation**

The efficacy and safety of nimodipine in patients under 18 years of age have not been adequately investigated. This information should be included in the product information, as proposed by the MAH:

> ***Dosage and method of administration – Special populations:***
> *Safety and efficacy of nimodipine in patients under 18 years of age have not been established.*

No further action is required.

# VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

*T*

| Member State Initials | Name of MAH | Name of Product | Pharmaceutical form(s) | Strength(s) |
|---|---|---|---|---|
| AT | Bayer Austria GmbH, Austria | Nimotop 30 mg - Filmtabletten | Film-coated tablet | 30 mg |
| BE | Bayer SA NV, Belgium | NIMOTOP | Film-coated tablet | 30 mg |
| BG | Bayer Pharma AG, Germany | NIMOTOP S | Film-coated tablet | 30 mg |
| CY | Bayer Hellas SA, Greece | Nimotop | Film-coated tablet | 30 mg |
| CZ | Bayer Pharma AG, Germany | NIMOTOP S | Film-coated tablet | 30 mg |
| DK | Bayer Pharma AG, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| EE | Bayer Pharma AG, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| FI | Bayer Pharma AG, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| FR | Bayer Sante SAS, France | NIMOTOP | Film-coated tablet | 30 mg |
| FR | Bayer Sante SAS, France | NIMOTOP | Film-coated tablet | 30 mg |
| FR | Bayer Sante SAS, France | NIMOTOP | Film-coated tablet | 30 mg |
| FR | Bayer Sante SAS, France | NIMOTOP | Film-coated tablet | 30 mg |
| FR | Bayer Sante SAS, France | NIMOTOP | Film-coated tablet | 30 mg |
| FR | Bayer Sante SAS, France | NIMOTOP | Film-coated tablet | 30 mg |
| DE | Bayer Vital GmbH, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| DE | Bayer Vital GmbH, Germany | NIMOTOP S | Film-coated tablet | 30 mg |
| GR | Bayer Hellas SA, Greece | NIMOTOP | Film-coated tablet | 30 mg |
| HR | Bayer Doo, Croatia | NIMOTOP | Film-coated tablet | 30 mg |
| HU | Bayer Pharma AG, Germany | Nimotop | Film-coated tablet | 30 mg |
| IE | Bayer Ltd, Ireland | NIMOTOP | Film-coated tablet | 30 mg |
| IT | Bayer SpA, Italy | NIMOTOP | Film-coated tablet | 30 mg |
| LV | Bayer Pharma AG, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| LU | Bayer SA NV, Belgium | NIMOTOP | Film-coated tablet | 30 mg |
| NL | Bayer BV, Netherlands | NIMOTOP | Film-coated tablet | 30 mg |

| Member State Initials | Name of MAH | Name of Product | Pharmaceutical form(s) | Strength(s) |
|---|---|---|---|---|
| NO | Bayer Pharma AG, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| PL | Bayer Pharma AG, Germany | NIMOTOP S | Film-coated tablet | 30 mg |
| PT | Bayer Portugal SA, Portugal | NIMOTOP | Film-coated tablet | 30 mg |
| RO | Bayer Pharma AG, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| SI | Bayer d.o.o, Slovenia | NIMOTOP | Film-coated tablet | 30 mg |
| SI | Bayer d.o.o, Slovenia | NIMODIPIN BAYER | Film-coated tablet | 30 mg |
| ES | Bayer Hispania SL, Spain | Nimotop | Film-coated tablet | 30 mg |
| SE | Bayer Pharma AG, Germany | NIMOTOP | Film-coated tablet | 30 mg |
| GB | Bayer Plc, United Kingdom | Nimotop 30mg Tablets | Film-coated tablet | 30 mg |
| IT | Bayer SpA, Italy | NIMOTOP | Oral drops | 4% |
| AT | Bayer Austria GmbH, Austria | Nimotop 10 mg - Infusionsflaschen | Solution for infusion | 10 mg/50 ml |
| BE | Bayer SA NV, Belgium | Nimotop 10mg/50ml solution | Solution for infusion | 10 mg/50 ml |
| BG | Bayer Pharma AG, Germany | NIMOTOP S | Solution for infusion | 10 mg/50 ml |
| CY | Bayer Hellas SA, Greece | Nimotop | Solution for infusion | 10 mg/50 ml |
| DK | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| EE | Bayer Pharma AG, Germany | NIMOTOP 0,2 MG/ML | Solution for infusion | 10 mg/50 ml |
| FI | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| FR | Bayer Sante SAS, France | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| FR | Bayer Sante SAS, France | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| DE | Bayer Vital GmbH, Germany | NIMOTOP S | Solution for infusion | 10 mg/50 ml |
| GR | Bayer Hellas SA, Greece | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| HR | Bayer Doo, Croatia | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| HU | Bayer Pharma AG, Germany | Nimotop | Solution for infusion | 10 mg/50 ml |
| HU | Bayer Pharma AG, Germany | Nimotop | Solution for infusion | 10 mg/50 ml |
| IE | Bayer Ltd, Ireland | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| IT | Bayer SpA, Italy | NIMOTOP | Solution for infusion | 10 mg/50 ml |

| Member State Initials | Name of MAH | Name of Product | Pharmaceutical form(s) | Strength(s) |
|---|---|---|---|---|
| LV | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| LU | Bayer SA NV, Belgium | Nimotop 10mg/50ml solution | Solution for infusion | 10 mg/50 ml |
| MT | Bayer Plc, United Kingdom | Nimotop 0.02% Solution for Infusion | Solution for infusion | 10 mg/50 ml |
| NL | Bayer BV, Netherlands | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| NO | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| PL | Bayer Pharma AG, Germany | NIMOTOP S | Solution for infusion | 10 mg/50 ml |
| PT | Bayer Portugal SA, Portugal | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| RO | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| SI | Bayer d.o.o, Slovenia | NIMOTOP S | Solution for infusion | 10 mg/50 ml |
| ES | Bayer Hispania SL, Spain | Nimotop | Solution for infusion | 10 mg/50 ml |
| SE | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 10 mg/50 ml |
| GB | Bayer Plc, United Kingdom | Nimotop 0.02% Solution for Infusion | Solution for infusion | 10 mg/50 ml |
| DK | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 50 mg/250 ml |
| NO | Bayer Pharma AG, Germany | NIMOTOP | Solution for infusion | 50 mg/250 ml |
| SE | Bayer Pharma AG, Germany | Nimotop | Solution for infusion | 50 mg/250 ml |