Please see full prescribing information for Nymalize® (nimodipine) Oral Solution
Dear Healthcare Professional:

Thank you for considering the inclusion of Nymalize® (nimodipine) Oral Solution on your formulary. This kit provides information to support informed decision making about the use of Nymalize in the clinical setting.

Nymalize is a dihydropyridine calcium channel blocker indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms, regardless of their post-ictus neurological condition (that is, Hunt and Hess grades I through V).1

It is important to note that blood pressure should be carefully monitored throughout treatment with Nymalize. The risk of hypotension may be increased with concurrent use of antihypertensives or CYP3A4 moderate or weak inhibitors. Patients with cirrhosis may be at an increased risk of adverse events. Concomitant use of Nymalize with strong CYP3A4 inhibitors or inducers should generally be avoided.1 Please see additional enclosed important safety information and full prescribing information.

Nymalize is the only oral nimodipine solution approved by the US Food and Drug Administration (FDA). Nimodipine was previously available only as a liquid-filled gel capsule. In the past, the need to extract the liquid from oral capsules for SAH patients unable to swallow has led to inadvertent IV administration of nimodipine, resulting in serious and sometimes fatal consequences for patients. Because of numerous serious errors reported in recent years, the FDA has acknowledged the risks associated with erroneous intravenous administration of nimodipine and issued several warnings concerning the administration of nimodipine liquid extracted from oral capsules.2-4 In these communications, the FDA identified patients who were unconscious or could not swallow nimodipine capsules as those who were at the highest risk for these medication errors. The notices also highlighted the benefit of using Nymalize in these patients because its availability as a ready-to-use oral solution eliminates the need for parenteral syringes.4

The Institute for Safe Medication Practices (ISMP) has also acknowledged the risks of capsule extraction and recommends that hospitals currently extracting nimodipine from capsules use Nymalize when a liquid form of nimodipine is needed.5

**Nymalize Oral Solution offers the following benefits:**

- Nymalize eliminates the need for needle extraction of nimodipine from capsules, which may help to reduce potentially fatal medication errors.
- Nymalize provides accurate, consistent dosing in a ready-to-use form.
- Nymalize provides a way for healthcare providers to administer the standard of care for SAH with greater safety and ease of use.

The indicated dosage of oral nimodipine therapy in patients with subarachnoid hemorrhage is 60 mg every 4 hours for 21 consecutive days. Patients with cirrhosis should be given a reduced dosage of 10 mL (30 mg) every 4 hours. Nymalize is available as a 16 ounce bottle and as a carton of twelve individually wrapped 10 mL or 20 mL unit dose cups. Each 10 mL unit dose cup contains 30 mg of nimodipine. Each 20 mL unit dose cup contains 60 mg of nimodipine.

The FDA approval of Nymalize was based on clinical studies evaluating the use of nimodipine oral capsules in patients with SAH. The most common adverse events observed in clinical studies with nimodipine were hypotension, headache, nausea, and bradycardia. Please review the full prescribing information enclosed in this kit.

(continued on next page)
Again, thank you for considering the inclusion of Nymalize® (nimodipine) Oral Solution on your formulary. For more information, please contact the Arbor Pharmaceuticals customer service team (email: customerservice@arborpharma.com; phone: 866.516.4950).

Sincerely,

Edward J. Schutter, RPh, MBA
President & Chief Executive Officer
Arbor Pharmaceuticals, LLC
www.arborpharma.com
www.nymalize.com


FORMULARY INFORMATION CONTENTS

Full Prescribing Information

Nymalize Product Fact Sheet

FDA Warnings About Nimodipine Medication Errors

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Questions & Answers About Nymalize

Please see full prescribing information for Nymalize® (nimodipine) Oral Solution
Please see full prescribing information for Nymalize® (nimodipine) Oral Solution
1 INDICATIONS AND USAGE
NYMALIZE is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I–V).

2 DOSAGE AND ADMINISTRATION
2.1 Administration Instructions
Administer only enterally (e.g., oral, nasogastric tube, or gastric tube route). Do not administer intravenously or by other parenteral routes. For all routes of administration, begin NYMALIZE within 96 hours of the onset of SAH. Administer one hour before a meal or two hours after a meal for all routes of administration [see Clinical Pharmacology (12.3)].

2.2 Administration by Oral Route
The recommended oral dosage is 20 mL (60 mg) every 4 hours for 21 consecutive days.

2.3 Administration Via Nasogastric or Gastric Tube
Using the supplied oral syringe labeled “ORAL USE ONLY,” administer 20 mL (60 mg) every 4 hours into a nasogastric or gastric tube for 21 consecutive days. For each dose, refill the syringe with 20 mL of 0.9% saline solution and then flush any remaining contents from nasogastric or gastric tube into the stomach.

2.4 Dosage Adjustments in Patients with Cirrhosis
In patients with cirrhosis, reduce the dosage to 10 mL (30 mg) every 4 hours [see Warnings and Precautions (5.2), Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS
Oral Solution (3 mg per mL):
• 60 mg per 20 mL, pale yellow solution
• 30 mg per 10 mL, pale yellow solution

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hypotension
Blood pressure should be carefully monitored during treatment with NYMALIZE. In clinical studies of patients with subarachnoid hemorrhage, about 5% of nimodipine-treated patients compared to 1% of placebo-treated patients had hypotension and about 1% of nimodipine-treated patients left the study because of this [see Adverse Reactions (6)].

5.2 Possible Increased Risk of Adverse Reactions in Patients with Cirrhosis
Given that the plasma levels of nimodipine are increased in patients with cirrhosis, these patients are at higher risk of adverse reactions. Therefore, monitor blood pressure and pulse rate closely and administer a lower dosage [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].
5.3 Possible Increased Risk of Hypotension with Strong CYP3A4 Inhibitors

Concomitant use of strong inhibitors of CYP3A4, such as some macrolide antibiotics (e.g., clarithromycin, telithromycin), some HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, saquinavir), some HCV protease inhibitors (e.g., boceprevir, telaprevir), some azole antifungals (e.g., ketoconazole, itraconazole, posaconazole, voriconazole), conivaptan, delavirdine, and nefazodone with nimodipine should generally be avoided because of a risk of significant hypotension [see Drug Interactions (7.2)].

5.4 Possible Reduced Efficacy with Strong CYP3A4 Inducers

Concomitant use of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, St John’s wort) and nimodipine should generally be avoided, as nimodipine plasma concentration and efficacy may be significantly reduced [see Drug Interactions (7.3)].

6 ADVERSE REACTIONS

The safety and efficacy of NYMALIZE (nimodipine oral solution) in the treatment of patients with SAH is based on adequate and well-controlled studies of nimodipine oral capsules in patients with SAH. NYMALIZE (nimodipine oral solution) has comparable bioavailability to nimodipine oral capsules.

The following clinically significant adverse reaction appears in other sections of the labeling:

- Hypotension [see Warnings and Precautions (5.1)].
### Table 1: Adverse Events [n (%)] reported with a frequency >1% in four clinical trials (Study 1, Study 2, Study 3, and Study 4)

<table>
<thead>
<tr>
<th>Nimodipine Dose Every 4 Hours</th>
<th>Placebo (n = 479)</th>
<th>0.35 mg/kg (n = 82)</th>
<th>30 mg (n = 71)</th>
<th>60 mg (n = 494)</th>
<th>90 mg (n = 172)</th>
<th>120 mg (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Blood Pressure</td>
<td>6 (1.2)</td>
<td>1 (1.2)</td>
<td>0</td>
<td>19 (3.8)</td>
<td>14 (8.1)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>Edema</td>
<td>3 (0.6)</td>
<td>0</td>
<td>0</td>
<td>2 (0.4)</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (0.6)</td>
<td>0</td>
<td>3 (4.2)</td>
<td>0</td>
<td>3 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (0.6)</td>
<td>2 (2.4)</td>
<td>0</td>
<td>3 (0.6)</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1 (1.4)</td>
<td>6 (1.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td>0</td>
<td>2 (2.4)</td>
<td>0</td>
<td>0</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (1.2)</td>
<td>1 (1.4)</td>
<td>6 (1.2)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EKG Abnormalities</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (1.0)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle Pain/Cramp</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0</td>
<td>1 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SAH is frequently accompanied by alterations in consciousness that may lead to an under-reporting of adverse experiences. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed in SAH trials.
7 DRUG INTERACTIONS

7.1 Blood Pressure Lowering Drugs

Nimodipine may increase the blood pressure lowering effect of concomitantly administered anti-hypertensives such as diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers, other calcium channel blockers, α-adrenergic blockers, PDE5 inhibitors, and α-methyldopa. In Europe, nimodipine was observed to occasionally intensify the effect of antihypertensive drugs taken concomitantly by hypertensive patients; this phenomenon was not observed in North American clinical trials. Blood pressure should be carefully monitored, and dose adjustment of the blood pressure lowering drug(s) may be necessary.

7.2 CYP3A4 Inhibitors

Nimodipine plasma concentration can be significantly increased when concomitantly administered with strong CYP3A4 inhibitors. As a consequence, the blood pressure lowering effect may be increased. Therefore, the concomitant administration of NYMALIZE and strong CYP3A4 inhibitors should generally be avoided [see Warnings and Precautions (5.3)]. Strong CYP3A4 inhibitors include some members of the following classes:

- macrolide antibiotics (e.g., clarithromycin, telithromycin),
- HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, saquinavir),
- HCV protease inhibitors (e.g., boceprevir, telaprevir),
-azole antimycotics (e.g., ketoconazole, itraconazole, posaconazole, voriconazole),
- conivaptan, delavirdine, nefazodone

Nimodipine plasma concentration can also be increased in the presence of moderate and weak inhibitors of CYP3A4. If nimodipine is concomitantly administered with these drugs, blood pressure should be monitored, and a reduction of the nimodipine dose may be necessary. Moderate and weak CYP3A4 inhibitors include alprozalam, ameneprevir, amiodarone, aprepitant, atazanavir, cimetidine, cyclosporine, diltiazem, erythromycin, fluconazole, fluoxetine, isoniazid, oral contraceptives, quinuprestin/dalfopristin, valproic acid, and verapamil.

A study in eight healthy volunteers has shown a 50% increase in mean peak nimodipine plasma concentrations and a 90% increase in mean area under the curve, after a one-week course of cimetidine at 1,000 mg/day and nimodipine at 90 mg/day. This effect may be mediated by the known inhibition of hepatic cytochrome P-450 (CYP) by cimetidine, which could decrease first-pass metabolism of nimodipine.

Grapefruit juice inhibits CYP3A4. Ingestion of grapefruit/grapefruit juice is not recommended while taking nimodipine.

7.3 CYP3A4 Inducers

Nimodipine plasma concentration and efficacy may be significantly reduced when concomitantly administered with strong CYP3A4 inducers. Therefore, concomitant use of NYMALIZE with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort) should generally be avoided [see Warnings and Precautions (5.4)].
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. NYMALIZE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nimodipine has been shown to have a teratogenic effect in two studies in rabbit. In one study, incidences of malformations and stunted fetuses were increased at oral doses of 1 mg/kg/day and 10 mg/kg/day administered throughout organogenesis but not at 3 mg/kg/day. In the second study, an increased incidence of stunted fetuses was seen at 1 mg/kg/day but not at higher doses (3 mg/kg/day and 10 mg/kg/day). Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses in rats at 100 mg/kg/day administered orally throughout organogenesis. In two other rat studies, doses of 30 mg/kg/day nimodipine administered orally throughout organogenesis and continued until sacrifice (day 20 of pregnancy or day 21 postpartum) were associated with higher incidences of skeletal variation, stunted fetuses, and stillbirths but no malformations.

8.3 Nursing Mothers

Nimodipine and/or its metabolites have been detected in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NYMALIZE, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of nimodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they had a different clinical response than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dosing in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy [see Clinical Pharmacology (12.3)].
10 OVERDOSAGE
There have been no reports of overdosage from the oral administration of nimodipine. Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to nimodipine overdosage may require active cardiovascular support with pressor agents and specific treatments for calcium channel blocker overdose. Since nimodipine is highly protein-bound, dialysis is not likely to be of benefit.

11 DESCRIPTION
NYMALIZE contains nimodipine, a dihydropyridine calcium channel blocker. Nimodipine is isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate. It has a molecular weight of 418.5 and a molecular formula of C_{21}H_{26}N_{2}O_{7}. The structural formula is:

![Nimodipine structural formula]

Nimodipine is a yellow crystalline substance, practically insoluble in water.

NYMALIZE Oral Solution contains 60 mg of nimodipine per 20 mL. In addition, the oral solution contains the following inactive ingredients: ethanol, glycerin, methylparaben, polyethylene glycol, sodium phosphate monobasic, sodium phosphate dibasic, and water.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Nimodipine is a dihydropyridine calcium channel blocker. The contractile processes of smooth muscle cells are dependent upon calcium ions, which enter these cells during depolarization as slow ionic transmembrane currents. Nimodipine inhibits calcium ion transfer into these cells and thus inhibits contractions of vascular smooth muscle. In animal experiments, nimodipine had a greater effect on cerebral arteries than on arteries elsewhere in the body perhaps because it is highly lipophilic, allowing it to cross the blood-brain barrier; concentrations of nimodipine as high as 12.5 ng/mL have been detected in the cerebrospinal fluid of nimodipine-treated SAH patients.

The precise mechanism of action of nimodipine in reducing the incidence and severity of ischemic deficits in adult patients with SAH from ruptured intracranial berry aneurysms is unknown. Although the clinical studies demonstrate a favorable effect of nimodipine on the severity of neurological deficits caused by cerebral vasospasm following SAH, there is no arteriographic evidence that nimodipine either prevents or relieves the spasm of these arteries. However, whether or not the arteriographic methodology utilized was adequate to detect a clinically meaningful effect, if any, on vasospasm is unknown.
12.3 Pharmacokinetics

In humans, nimodipine is rapidly absorbed after oral administration, and peak concentrations are generally attained within one hour. The terminal elimination half-life is approximately 8 to 9 hours but earlier elimination rates are much more rapid, equivalent to a half-life of 1-2 hours; a consequence is the need for frequent (every 4 hours) dosing. There were no signs of accumulation when nimodipine was given three times a day for seven days. Nimodipine is over 95% bound to plasma proteins. The binding was concentration independent over the range of 10 ng/mL to 10 mcg/mL. Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. Numerous metabolites, all of which are either inactive or considerably less active than the parent compound, have been identified. The metabolism of nimodipine is mediated by CYP3A4. Because of a high first-pass metabolism, the bioavailability of nimodipine averages 13% after oral administration.

Food Effects

In a study of 24 healthy male volunteers, administration of nimodipine capsules following a standard breakfast resulted in a 68% lower peak plasma concentration and 38% lower bioavailability relative to dosing under fasted conditions [see Dosage and Administration (2.1)].

Patients with Cirrhosis

The bioavailability of nimodipine is significantly increased in patients with cirrhosis, with Cmax approximately double that in normals which necessitates lowering the dose in this group of patients [see Dosage and Administration (2.4), Warnings and Precautions (5.2)].

Geriatric Patients

In a single parallel-group study involving 24 elderly subjects (aged 59-79) and 24 younger subjects (aged 22-40), the observed AUC and Cmax of nimodipine was approximately 2-fold higher in the elderly population compared to the younger study subjects following oral administration (given as a single dose of 30 mg and dosed to steady-state with 30 mg three times daily for 6 days). The clinical response to these age-related pharmacokinetic differences, however, was not considered significant. [see Use in Specific Populations, Geriatric Use (8.5)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a two-year study in rat, the incidences of adenocarcinoma of the uterus and Leydig cell adenoma of the testes were increased at 1800 ppm nimodipine in the diet (approximately 90-120 mg/kg/day). The increases were not statistically significant, however, and the higher rates were within the historical control range for these tumors. Nimodipine was found not to be carcinogenic in a 91-week mouse study, but the high dose of 1800 ppm nimodipine in the diet (approximately 550-775 mg/kg/day) was associated with an increased mortality rate.

Mutagenesis

Mutagenicity studies, including the Ames, micronucleus, and dominant lethal assays, were negative.
Impairment of Fertility

Nimodipine did not impair the fertility and general reproductive performance of male and female rats following oral doses of up to 30 mg/kg/day when administered prior to mating and continuing in females to day 7 of pregnancy. This dose in a rat is similar to a clinical dose of 60 mg every 4 hours in a 60 kg patient, on a body surface area (mg/m²) basis.

14 CLINICAL STUDIES

The safety and efficacy of NYMALIZE (nimodipine oral solution) in the treatment of patients with SAH is based on adequate and well-controlled studies of nimodipine oral capsules in patients with SAH. NYMALIZE (nimodipine oral solution) has comparable bioavailability to nimodipine oral capsules.

Nimodipine has been shown in 4 randomized, double-blind, placebo-controlled trials to reduce the severity of neurological deficits resulting from vasospasm in patients who have had a recent SAH (Studies 1, 2, 3, and 4).

The trials used doses ranging from 20-30 mg to 90 mg every 4 hours, with drug given for 21 days in 3 studies, and for at least 18 days in the other. Three of the four trials followed patients for 3-6 months. Three of the trials studied relatively well patients, with all or most patients in Hunt and Hess Grades I – III (essentially free of focal deficits after the initial bleed). Study 4 studied much sicker patients, with Hunt and Hess Grades III – V. Studies 1 and 2 were similar in design, with relatively unimpaired SAH patients randomized to nimodipine or placebo. In each, a judgment was made as to whether any late-developing deficit was due to spasm or other causes, and the deficits were graded. Both studies showed significantly fewer severe deficits due to spasm in the nimodipine group; Study 2 showed fewer spasm-related deficits of all severities. No effect was seen on deficits not related to spasm. See Table 2.

Table 2: Deficits in Patients with Hunt and Hess Grades I to III in Study 1 and Study 2

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Number Analyzed</th>
<th>Number of Patients with Any Deficit Due to Spasm</th>
<th>Numbers with Severe Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>I – III</td>
<td>Nimodipine 20–30 mg every 4 hours</td>
<td>56</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>60</td>
<td>16</td>
</tr>
<tr>
<td>Study 2</td>
<td>III – V</td>
<td>Nimodipine 60 mg every 4 hours</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>39</td>
<td>11</td>
</tr>
</tbody>
</table>

*Hunt and Hess Grade

**p = 0.03
Study 3 was a 554-patient trial that included SAH patients with all grades of severity (89% were in Hunt and Hess Grades I-III). In Study 3, patients were treated with placebo or 60 mg of nimodipine every 4 hours. Outcomes were not defined as spasm related or not but there was a significant reduction in the overall rate of brain infarction and severely disabling neurological outcome at 3 months (Table 3).

Study 4 enrolled much sicker patients (Hunt and Hess Grades III-V), who had a high rate of death and disability and used a dose of 90 mg every 4 hours, but was otherwise similar to Study 1 and Study 2. Analysis of delayed ischemic deficits, many of which result from spasm, showed a significant reduction in spasm-related deficits. Among analyzed patients (72 nimodipine, 82 placebo), there were the following outcomes (Table 4).

### Table 3: Degree of Recovery or Disability in Study 3 (89% Hunt and Hess Grades I-III)

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>278</td>
<td>276</td>
</tr>
<tr>
<td>Good recovery</td>
<td>199*</td>
<td>169</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Severe disability</td>
<td>12**</td>
<td>31</td>
</tr>
<tr>
<td>Death</td>
<td>43***</td>
<td>60</td>
</tr>
</tbody>
</table>

*\(p = 0.001\) – severe disability
**\(p = 0.056\) – death

### Table 4: Neurological Ischemic Deficits in Study 4 (Hunt and Hess Grades III-V)

<table>
<thead>
<tr>
<th></th>
<th>Delayed Ischemic Deficits (DID)</th>
<th>Permanent Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nimodipine 90 mg every 4 hours n (%)</td>
<td>Placebo n (%)</td>
</tr>
<tr>
<td>DID Spasm Alone</td>
<td>8 (11)*</td>
<td>25 (31)</td>
</tr>
<tr>
<td>DID Spasm Contributing</td>
<td>18 (25)</td>
<td>21 (26)</td>
</tr>
<tr>
<td>DID Without Spasm</td>
<td>7 (10)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>No DID</td>
<td>39 (54)</td>
<td>28 (34)</td>
</tr>
</tbody>
</table>

*\(p = 0.001\), Nimodipine versus placebo
When data were combined for Study 3 and Study 4, the treatment difference on success rate (i.e., good recovery) on the Glasgow Outcome Scale was 25.3% (nimodipine) versus 10.9% (placebo) for Hunt and Hess Grades IV or V. Table 5 demonstrates that nimodipine tends to improve good recovery of SAH patients with poor neurological status post-ictus, while decreasing the numbers with severe disability and vegetative survival.

### Table 5: Glasgow Outcome Scale in Combined Studies 3 and 4

<table>
<thead>
<tr>
<th>Glasgow Outcome*</th>
<th>Nimodipine (n = 87)</th>
<th>Placebo (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good recovery</td>
<td>22 (25.3%)</td>
<td>11 (10.9%)</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>8 (9.2%)</td>
<td>12 (11.9%)</td>
</tr>
<tr>
<td>Severe disability</td>
<td>6 (6.9%)</td>
<td>15 (14.9%)</td>
</tr>
<tr>
<td>Vegetative Survival</td>
<td>4 (4.6%)</td>
<td>9 (8.9%)</td>
</tr>
<tr>
<td>Death</td>
<td>47 (54%)</td>
<td>54 (53.5%)</td>
</tr>
</tbody>
</table>

*p = 0.045, nimodipine vs. placebo

A dose ranging study comparing 30 mg, 60 mg, and 90 mg doses found a generally low rate of spasm-related neurological deficits but no dose response relationship.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Nymalize (nimodipine) Oral Solution 3 mg/mL is a pale yellow solution and is supplied as follows:

- NDC 24338-200-16: 16 oz. bottle (473 mL) 60 mg/20 mL
- NDC 24338-200-12: Carton containing 12 individually wrapped 20 mL packages. Each package contains one 60 mg/20 mL Unit-Dose cup (NDC 24338-200-20) and one oral syringe.
- NDC 24338-205-12: Carton containing 12 individually wrapped 10 mL packages. Each package contains one 30 mg/10 mL Unit-Dose cup (NDC 24338-205-10) and one oral syringe.

Store at 25ºC (77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP Controlled Room Temperature].

Protect from light.

Do not refrigerate.
17 PATIENT COUNSELING INFORMATION

Inform patients that the most frequent adverse reaction associated with nimodipine is decreased blood pressure [see Warnings and Precautions (5.1)]. Inform them that use of NYMALIZE with anti-hypertensives can cause increased drop in blood pressure [see Drug Interactions (7.1)].

Patients should be aware that ingestion of grapefruit or grapefruit juice should be avoided when taking NYMALIZE due to its ability to increase nimodipine plasma concentrations and potential to increase the risk of hypotension [see Drug Interactions (7.2)].

Pregnant women should be advised that a harmful effect of NYMALIZE on the fetus cannot be ruled out and the drug should only be used if the potential benefit justifies the potential risk to the fetus [see Use in Specific Populations, Pregnancy (8.1)].

Manufactured for:

Manufactured by:

Importfab
Pointe-Claire, QC, Canada
H9R 1C9

Distributed by
Arbor Pharmaceuticals, LLC Atlanta, GA 30328

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NIM-PI-04
Please see full prescribing information for Nymalize® (nimodipine) Oral Solution
Nymalize® (nimodipine) Oral Solution

MANUFACTURED BY
Importfab
Pointe-Claire, QC, Canada  H9R 1C9

MARKETED BY
Arbor Pharmaceuticals, LLC, Atlanta, GA 30328
Phone: 866-516-4950
Internet: www.arborpharma.com
www.nymalize.com

PRODUCT NAME
Nymalize® (Oral Solution)

ESTABLISHED NAME
(nimodipine)

NDC CODE
24338-200-16 (16 oz bottle)
24338-200-12 (Carton of 12, 20 mL unit dose cups)
24338-200-20 (individual unit dose cup)
24338-205-12 (Carton of 12, 10 mL unit dose cups)
24338-205-10 (individual unit dose cup)

MINIMUM ORDER QUANTITY
1 16 oz (473 mL) bottle
1 carton of 12, 20 mL (60 mg) unit dose cups
1 carton of 12, 10 mL (30 mg) unit dose cups

HOW TO ORDER
Ordering available through wholesalers

HOW SUPPLIED
16 oz (473 mL) bottle
1 carton of 12, 20 mL (60 mg) unit dose cups
1 carton of 12, 10 mL (30 mg) unit dose cups

DATED ITEMS
The expiration date is printed on each carton, cup, and bottle

PRESCRIPTION LEGEND
Prescription only

SPECIAL STORAGE REQUIREMENTS
Store between 20°C to 25°C (68°F to 77°F)
Excursions permitted to 15°C to 30°C (59°F to 86°F)
Protect from light
Do not refrigerate

PRODUCT INFORMATION
For medical information:
Phone: 866-516-4950
E-mail: medinfo@arborpharma.com

To report an adverse event:
Phone: 866-516-4950
E-mail: aereports@arborpharma.com

DOSAGE
Each 20 mL of Nymalize contains 60 mg of nimodipine
Each 10 mL of Nymalize contains 30 mg of nimodipine

Please see full prescribing information for Nymalize® (nimodipine) Oral Solution
FDA WARNINGS ABOUT NIMODIPINE MEDICATION ERRORS

Please see full prescribing information for Nymalize® (nimodipine) Oral Solution
FDA Warnings About Nimodipine Medication Errors

Introduction

The indicated dosage of oral nimodipine therapy in patients with subarachnoid hemorrhage (SAH) is 60 mg every 4 hours for 21 consecutive days, preferably not less than 1 hour before or 2 hours after meals. Oral nimodipine therapy should ideally start within 96 hours of the SAH.

Nimodipine should be given only by mouth or by way of enteral administration. This oral medication should never be given by intravenous or parenteral administration.

The US Food and Drug Administration (FDA) requested that an oral solution of nimodipine be formulated.1 Nymalize® is the first oral solution of nimodipine approved by the FDA (Figure 1).2

Figure 1. FDA news release announcing the approval of Nymalize.2

FDA NEWS RELEASE May 14, 2013

FDA approves Nymalize — first nimodipine oral solution for use in certain brain hemorrhage patients

New oral formulation may help reduce potentially fatal medication errors

On May 10, the US Food and Drug Administration approved Nymalize, a new nimodipine oral solution, to treat patients experiencing symptoms resulting from ruptured blood vessels in the brain (subarachnoid hemorrhage). Nimodipine previously was available only as a liquid-filled gel capsule.

Subarachnoid hemorrhage is serious, life-threatening bleeding that occurs in the subarachnoid space — the area between the brain and the thin tissues that cover the brain. Nimodipine is a medication given in a critical care setting to treat neurologic complications from subarachnoid hemorrhage.

Over the years, the FDA has received reports of serious and sometimes fatal consequences from intravenous (IV) injection of the liquid contents of oral nimodipine capsules. IV administration of nimodipine meant for oral use can result in death, cardiac arrest, severe decrease in blood pressure, and other heart-related complications. In August 2010, the agency reminded healthcare professionals about the risks of IV administration of nimodipine from oral capsules, and in 2006 a Boxed Warning was added to the drug to warn against such use.

“Having an oral version of this product may help reduce the medication errors we’ve seen from erroneous intravenous administration of the contents of oral capsules,” said Russell Katz, MD, director of the Division of Neurology Products in the FDA’s Center for Drug Evaluation and Research. “Nymalize is a liquid that is administered orally, or via nasogastric tube or gastric tube, and there is no need for a needle to be used, which is what caused past medication errors.”

Based on the potential of the oral formulation, Nymalize, to decrease or eliminate medication errors, the application received fast track designation and priority review. Fast track and priority review are two programs the FDA uses to make drugs rapidly available.

The approval of Nymalize is based on clinical studies evaluating the use of nimodipine oral capsules in patients with subarachnoid hemorrhage. The most common adverse event observed in the studies was decreased blood pressure. A patient’s blood pressure should be carefully monitored during treatment.

Nymalize is made by Atlanta-based Arbor Pharmaceuticals, Inc.
**FDA Warnings About Nimodipine Medication Errors**

The Practice of Extracting Nimodipine From Capsules: Threat of Intravenous Administration

Some patients who suffer SAH are not able to swallow nimodipine in capsule or liquid form — in many cases due to the patients being unconscious. For these patients, nimodipine must be administered by means of nasogastric or gastric tube.

Before Nymalize was developed as an oral solution of nimodipine, caregivers — often nurses, sometimes pharmacists — had to perform needle extraction of the liquid from nimodipine capsules for enteral administration to patients who could not swallow the capsules.

This nimodipine liquid extraction process has been found to be time-consuming, complicated, and problematic. The instructions call for using an 18-gauge needle to pierce both ends of the nimodipine capsule. The liquid contents are then to be squeezed from the capsule or extracted with that same 18-gauge needle, which due to its size must be attached to an intravenous (not an oral) syringe labeled “Not for IV Use,” despite the fact that nimodipine should not be administered intravenously. The extracted liquid nimodipine is then to be transferred from the intravenous syringe to an oral syringe and then emptied into the patient’s in situ nasogastric tube (or other means of enteral administration) and washed down the tube with 30 mL of normal saline (0.9%).

Because each nimodipine capsule contains 30 mg of nimodipine, the process of nimodipine extraction requires frequent manual manipulations. For the full daily regimen of nimodipine for patients who must receive the drug by way of enteral administration, it is necessary to extract the medication from 12 30 mg capsules (2 30 mg capsules per dose for 6 doses per day).

Every such needle extraction of nimodipine liquid takes time and exposes the caregiver to the risk of needle stick. Because the manual extraction procedure invariably leaves some residue, there is no way to know the exact amount of the nimodipine dose being delivered. Data suggest that this extraction process may lead to a 25% dose reduction with each 60 mg dose.

The routine use of intravenous syringes to extract the liquid from capsules increases the risk that nimodipine might inadvertently be administered intravenously. Most patients who experience SAH are hospitalized in critical care units and are already receiving intravenous medications — a circumstance that contributes to the risk.

The extraction of nimodipine from capsule formulation by means of intravenous syringes has been associated with numerous reported adverse events, including death.

The use of Nymalize Oral Solution eliminates the need for extraction and the complications entailed in that process. Nymalize is available as a 16 ounce bottle and as a carton of twelve individually wrapped 10 mL or 20 mL unit dose cups. Each 10 mL unit dose cup contains 30 mg of nimodipine. Each 20 mL unit dose cup contains 60 mg of nimodipine.
FDA Warnings About Nimodipine Medication Errors

Food and Drug Administration Safety Warnings

From when nimodipine first became available on the market in 1988, through 2013, the FDA identified 36 cases of medication errors associated with the use of nimodipine. As originally detailed in an FDA Drug Safety Communication released in 2010 for healthcare providers, and then updated in an FDA notice released in 2014, 27 of those medication errors involved erroneous intravenous prescribing or administration of nimodipine. The results of the errors were catastrophic: 5 patients died, while several others had near-death events or suffered permanent harm.

Because nimodipine is an antihypertensive calcium-channel blocker, when the medication is delivered intravenously rather than orally, the effect can cause cardiovascular collapse and possibly death.

In 1996, the FDA requested that a bolded statement be added to the nimodipine prescribing information to warn against the incorrect administration of nimodipine.

Then, in 2006, the FDA added both a black-box warning and a warning to the nimodipine labeling to alert practitioners not to administer nimodipine intravenously or by other parenteral routes. This warning described the potential for fatal and life-threatening adverse effects following erroneous intravenous administration of nimodipine.

The FDA also requested that the manufacturer of nimodipine capsules issue a Dear Doctor letter to alert clinicians of the dangers associated with erroneous intravenous administration of nimodipine.

In addition, the FDA revised the Dosage and Administration section of the Prescribing Information regarding administration of the capsule contents to patients who are unable to swallow. One of these changes was the recommendation that the intravenous syringe used to extract nimodipine from capsules be labeled “Not for IV Use.”

Then in August 2010, the FDA issued the Drug Safety Communication warning about serious medication errors from the intravenous administration of nimodipine oral capsules. That warning is reproduced in Figure 2.

In February 2013, an issue of ISMP Medication Safety Alert from the Institute for Safe Medication Practices (ISMP), which is not affiliated with the FDA, reported on a recent death due to this cause in an SAH patient with a nasogastric tube. In another newsletter released later in July of 2013, the ISMP recommended that hospitals currently extracting nimodipine from capsules should use Nymalize when a liquid form of nimodipine is needed.

In an FDA notice released in April 2014, the FDA further acknowledged the risks associated with erroneous intravenous administration of nimodipine and described those patients who are at greatest risk (Figure 3), adding that they are “the patients who are the most vulnerable to the medication errors identified.” These patients are typically unconscious and/or cannot swallow. The same FDA notice went further to highlight the benefit of Nymalize in these patients, as it eliminates the need for a parenteral syringe (Figure 3).

However, despite steps by the FDA to prevent medication errors associated with capsule extraction of liquid nimodipine, the threat of serious consequences from inadvertent intravenous administration persists. This may be contributed to by the ongoing use of capsule extraction for patients who are unconscious and cannot swallow.
FDA Drug Safety Communication:
Serious medication errors from intravenous administration of nimodipine oral capsules

Safety Announcement
[08-02-2010] The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals that nimodipine capsules should be given ONLY by mouth or through a feeding tube (nasogastric tube). This oral medication should NEVER be given by intravenous administration. FDA continues to receive reports of intravenous nimodipine use, with serious, sometimes fatal, consequences. Intravenous injection of nimodipine can result in death, cardiac arrest, severe falls in blood pressure, and other heart-related complications.

Nimodipine is a medication intended to be given in a critical care setting to treat neurologic complications from subarachnoid hemorrhage (ruptured blood vessels in the brain) and is only available as a capsule.

In 2006, FDA added a Boxed Warning and made other revisions to the prescribing information to warn against intravenous use of nimodipine. The prescribing information also provides clear instructions on how to remove the liquid contents from the capsules for nasogastric tube administration in patients who are unable to swallow. The instructions recommend that the syringe used for withdrawal of capsule contents be labeled with “Not for IV Use.”

FDA will continue working with the manufacturers of nimodipine and with outside groups to evaluate and implement additional ways to prevent medication errors with this product.
Additional Information for Patients

- FDA encourages all patients to talk to their healthcare professional if they have concerns about any treatment they are receiving.
- Report any side effects from the use of medication to the FDA MedWatch program, using the information in the “Contact Us” box at the bottom of the page.

Additional Information for Healthcare Professionals

- Be aware that nimodipine should be administered ONLY by the oral route or via nasogastric tube. It should NEVER be administered intravenously.
- If the nimodipine capsule cannot be swallowed — e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. To help minimize administration errors, it is recommended that the syringe be labeled “Not for IV Use.” The needle should be removed from the syringe and the contents should then be emptied into the patient’s in situ nasogastric tube and washed down the tube with 30 mL of normal saline (0.9%).
- Report adverse events or medication errors involving nimodipine capsules to the FDA MedWatch program using the information in the “Contact Us” box at the bottom of this page.

Data Summary

Since the approval of nimodipine in 1988, FDA has taken several actions intended to reduce the occurrence of inappropriate intravenous use of this drug. In 1996, a bolded statement was added to the prescribing information to warn against incorrect administration of nimodipine. In 2006, FDA added both a Boxed Warning and a Warning to the nimodipine labeling to alert practitioners not to administer nimodipine intravenously or by other parenteral routes and described the potential for
FDA WARNINGS ABOUT NIMODIPINE MEDICATION ERRORS

FDA identified 31 cases of medication errors associated with the use of nimodipine that were reported to FDA’s Adverse Event Reporting System (AERS), the Pennsylvania Patient Safety Reporting System (PA-PSRS), the Institute for Safe Medication Practices’ (ISMP) Quantros MEDMARX database, and the Council for International Organizations of Medical Sciences (CIOMS) II database, and published in the medical literature between 1989 (initial marketing of nimodipine) and 2009. Of the 31 medication errors, 25 involved erroneous intravenous nimodipine prescribing or administration. Four of the patients who mistakenly received nimodipine intravenously died; five patients were characterized as having near-death events; and one patient was characterized as having suffered permanent harm as a result of the inadvertent intravenous administration of nimodipine.

Based on FDA’s review of these reports, the following factors have been identified as contributing to this preventable medication error:

- Since some patients receiving nimodipine cannot swallow the capsules they must receive the liquid from the capsules through a feeding tube. The nimodipine prescribing information has instructions for using a needle to make a hole in both ends of the capsule to remove the liquid contents with a syringe and then empty the contents into the feeding tube. Because a standard needle will not fit on an oral syringe, the needle must be attached to an intravenous syringe. The use of intravenous syringes to deliver nimodipine increases the chance that the medication will be given intravenously instead of by mouth or nasogastric tube.
- Most patients receiving nimodipine are hospitalized in critical care units and are already receiving intravenous medications.
Determination That NIMOTOP (Nimodipine) Capsules, 30 Milligrams, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

"In responding to the Petition, we have carefully reviewed our files for records concerning the withdrawal of NIMOTOP (Nimodipine) Capsules, 30 mg. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. The adverse event reports included 36 reports of medication errors associated with the administration or prescribing of nimodipine capsules, 30 mg, which were received between 1989 (the initial marketing of NIMOTOP) and November 2013. Of these 36 reports, 27 involved the erroneous intravenous administration of nimodipine. The intravenous injection of nimodipine can result in cardiac arrest, severe drop in blood pressure, other cardiac-related complications, and death. In almost all of the cases involving erroneous intravenous administration, there were serious or potentially serious outcomes, with 5 of the 27 cases resulting in the death of the patient. FDA has attributed these medication errors to the use of an intravenous needle and syringe at bedside to extract the capsule contents for administration to patients that are unconscious or cannot swallow the capsules. In such cases, the professional labeling instructions call for using an 18-gauge needle to make a hole on both ends of the capsule to extract the capsule's liquid contents into a syringe, and then administering the extracted liquid to the patient orally or via a nasogastric tube (feeding tube). Because a needle will not fit on an oral syringe, the health care provider must use a parenteral syringe to extract the liquid from the capsule. Once the drug is prepared in a parenteral syringe, rather than administering it orally or through a nasogastric tube as further directed in the drug's labeling, a conditioned response can occur where the drug is erroneously administered intravenously. Most patients receiving nimodipine capsules require complex care, are hospitalized in critical care units, and are receiving other intravenous medications, which may further contribute to the occurrence of such errors. Each year, between 20,000 and 30,000 patients in the United States are administered nimodipine for the emergency treatment of subarachnoid hemorrhage. Since NIMOTOP was approved in 1988, FDA has taken several actions to reduce these medication errors."
FDA Warnings about Nimodipine Medication Errors

These include labeling changes, a Dear Healthcare Professional Letter, two FDA Patient Safety News Webcasts, and a Drug Safety Communication. As recently as August 2010, FDA issued a safety alert, again emphasizing to health care professionals that nimodipine capsules should be given only by mouth or through a nasogastric tube and that they should never be given by intravenous administration. In addition, in February 2012, Barr Pharmaceuticals added the following statement to the labeling directing health care professionals to transfer the capsule contents to a syringe that cannot accept a needle: ‘A parenteral syringe can be used to extract the liquid inside the capsule, but the liquid should always be transferred to a syringe that cannot accept a needle and that is designed for administration orally or via a nasogastric tube or PEG.’ Despite these efforts by FDA and the drug’s sponsor, a small number of adverse events due to erroneous intravenous administration continue to be reported to the Agency. Nevertheless, FDA believes that it is in the best interest of the public health for patients to continue to have access to this lifesaving drug for a number of reasons. First, only a portion of the patients treated with nimodipine capsules are unconscious and unable to swallow—these are the patients who are most vulnerable to the medication errors identified. Of those patients that begin their course of treatment (two capsules every 4 hours for 21 days) while unable to swallow, many improve to the point where they are awake and able to swallow a capsule soon after treatment begins. Hence, for many patients, the risk of erroneous intravenous administration is only present during a small percentage of their overall duration of treatment.

Second, we believe the approval of a nimodipine oral solution that is administered via an oral syringe only will further prevent erroneous intravenous administration because it can be used for those patients who are unconscious or unable to swallow and eliminates the need for use of a parenteral syringe, which is the source of the medication errors. And third, we believe the capsules play an important role in treating patients with subarachnoid hemorrhage because many are discharged from the hospital while taking capsules, and capsules provide a more convenient route of administration that increases patient compliance.”
Summary

The FDA requested that an oral solution of nimodipine be formulated.\(^1\) Nymalize is the first oral solution of nimodipine approved by the FDA.\(^2\) The ISMP recommended that hospitals currently extracting nimodipine from capsules should use Nymalize when a liquid form of nimodipine is needed.\(^8\)

Nymalize is ready to use, requiring no needle extraction. The availability of Nymalize allows timely, accurate, and consistent dosing, without the inexactitude, complications, and dangers associated with needle extraction from nimodipine capsules for patients who cannot take the drug orally.

References


SELECTED PUBLISHED LITERATURE

Introduction

The published literature concerning the use of nimodipine for improvement of neurological outcome in patients with aneurysmal subarachnoid hemorrhage (aSAH) from ruptured intracranial berry aneurysms is extensive.

In the 2012 guidelines for health professionals on the management of aneurysmal subarachnoid hemorrhage from the American Heart Association and American Stroke Association, the use of oral nimodipine is a class I recommendation, with the level of evidence rated as A. The recommendation reads: “Oral nimodipine should be administered to all patients with aSAH.”¹

In this listing of published literature, selected articles about the management of aSAH and the use of nimodipine in treating aSAH patients have been sorted into five different categories:

Part 1. Recent guidelines concerning subarachnoid hemorrhage

Part 2. Randomized placebo-controlled trials of nimodipine for improvement of neurological outcomes in patients with subarachnoid hemorrhage

Part 3. Other studies of nimodipine in relationship to subarachnoid hemorrhage

Part 4. Recent meta-analyses and systematic reviews of nimodipine and/or vasospasm in patients with subarachnoid hemorrhage

Part 5. Recent review articles of the management of subarachnoid hemorrhage and/or the use of nimodipine in patients with subarachnoid hemorrhage

Part 1. Recent guidelines concerning subarachnoid hemorrhage*


*Literature search conducted April 2013.
Part 2. Randomized placebo-controlled trials of nimodipine for improvement of neurological outcomes in patients with subarachnoid hemorrhage


*Literature search conducted April 2013.
**Part 3. Other studies of nimodipine in relationship to subarachnoid hemorrhage**


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*Literature search conducted April 2013.
Selected Published Literature

Part 4. Recent meta-analyses and systematic reviews of nimodipine and/or vasospasm in patients with subarachnoid hemorrhage*


*Literature search conducted April 2013.
Part 5. Recent review articles of the management of subarachnoid hemorrhage and/or the use of nimodipine in patients with subarachnoid hemorrhage


Selected Published Literature


* Literature search conducted April 2013.
Questions & Answers About Nymalize

What is the indication for Nymalize?

Nymalize® (nimodipine) Oral Solution is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH) from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I–V).1

What is subarachnoid hemorrhage?

SAH, a form of stroke, designates bleeding into the subarachnoid space — a small area at the base of the brain containing blood vessels that supply the brain and spinal cord. The most common cause of SAH (approximately 85% of cases) is rupture of a small cerebral artery aneurysm. Besides the hallmark thunderclap headache, presenting symptoms of SAH can include nausea and/or vomiting, stiff neck, photophobia, brief loss of consciousness, and focal neurological deficits. The neurological condition of the patient, particularly the level of consciousness, is the most important determinant of outcome after SAH. Modes of diagnostic imaging for SAH include head computed tomography (CT), magnetic resonance (MR) brain imaging, and digital subtraction angiography (DSA). Sudden death occurs in 10% to 15% of individuals at the time of aneurysm rupture, and coma is common among survivors with extensive hemorrhage.2-5

The incidence of SAH worldwide has been estimated at upwards of 9 cases per 100,000 and has decreased only slightly over the last half century. The incidence increases with age, with a typical average age of onset of ≥50 years. Behavioral risk factors for aneurysmal SAH include hypertension, smoking, alcohol abuse, and the use of sympathomimetic drugs (for example, cocaine). The risk is increased by presence of unruptured cerebral aneurysm, history of previous SAH, family history, and certain genetic syndromes.3,4

Patients who survive the initial hours after SAH are at risk of deterioration from rebleeding, secondary ischemia (delayed cerebral ischemia [DCI]), hydrocephalus, and medical complications. The risk of rebleeding is greatest in the first 2 to 12 hours and is addressed with preventive medical treatment (including antifibrinolytic drugs) and by excluding the aneurysm by means of surgical clipping and/or endovascular coiling. DCI, a clinical syndrome of focal neurological and/or cognitive deficits, occurs in approximately one third of SAH patients, most often at 4 to 14 days after hemorrhage, and results in death or disability in approximately one half of those affected. In possibly 50% of cases, DCI may be attributed to delayed cerebral vasospasm (narrowing of intracranial arteries), which tends to occur during the same period following SAH and with similar diffuse manifestation. An increase of calcium in vascular smooth muscle cells is recognized as playing a significant role in the complex etiology of vasospasm.3-5
What is the recommended use of Nymalize (nimodipine) Oral Solution for SAH patients?

Treatment with oral nimodipine is a class IA recommendation for all patients with aneurysmal SAH in the latest SAH management guidelines from the American Heart Association and American Stroke Association. Nimodipine therapy should be initiated as soon as possible following SAH, preferably within 96 hours of ictus. Maintenance of euvolemia and normal circulating blood volume is a class IB recommendation for preventing DCI after SAH.

How does Nymalize Oral Solution differ from previous formulations of nimodipine in preventing secondary ischemia following SAH?

Nymalize is the first and only oral solution of nimodipine with the drug’s current indication. Prior to the introduction of Nymalize, since 1988, oral nimodipine was available in capsule formulation. Due in many cases to their being unconscious, some SAH patients are not able to swallow nimodipine — in the form of either oral solution or capsules. For these patients, enteral administration is required. Whereas the appropriate dose of Nymalize Oral Solution may be readily and accurately introduced into the feeding tube with an oral syringe, a more complicated, time-consuming, and inexact process is required to perform needle extraction from nimodipine capsules and then empty the liquid into the nasogastric tube (or other means of enteral administration) with an intravenous syringe. A documented issue with the needle extraction from nimodipine capsules is the threat of inadvertent intravenous administration of the drug, which can result in death, cardiac arrest, severe falls in blood pressure, and other heart-related complications.

How does oral nimodipine differ from other therapies for preventing secondary ischemia following SAH?

As a treatment for preventing secondary ischemia and poor outcomes for SAH patients, oral nimodipine differs from other calcium channel blockers in its ability to affect the central nervous system preferentially. A Cochrane review, including 16 trials with 3361 patients with SAH, found a relative risk of 0.81 (95% CI 0.72 to 0.92) for death or dependence in patients treated with calcium channel blockers. But analysis for poor outcome according to type of calcium antagonist and route of administration found statistically significant results only for oral nimodipine (relative risk 0.67, 95% CI 0.55 to 0.81). For other calcium channel blockers or intravenous administration of nimodipine the results in terms of improved neurological outcome were not statistically significant. The benefit of oral nimodipine has been attributed to the drug’s neuroprotective properties rather than its vasodilatory effects. The hemodynamic strategy referred to as triple-H therapy — consisting of induced hypotension, hypervolemia, and hemodilution — is widely used, but recent analyses have found no good evidence for a positive effect.
QUESTIONS & ANSWERS ABOUT NYMALIZE

What is the mode of action of Nymalize?

Unlike other dihydropyridine calcium channel blockers currently available, nimodipine appears to affect the central nervous system preferentially. The principal physiologic action of nimodipine is inhibition of the influx of extracellular calcium ions through voltage-dependent and receptor-operated slow calcium channels in the membranes of myocardial, vascular smooth muscle, and neuronal cells. The contractile processes of smooth muscle cells are dependent upon calcium ions. The exact mechanism of the calcium-ion inhibition by nimodipine is not known, but binding of the drug to specific high-affinity receptor sites on the cell membrane in or near the calcium channel may effect changes leading to a state in which the calcium channel is unavailable for opening.

Nimodipine has improved neurologic outcomes in SAH patients regardless of the angiographic presence or absence of vasospasm prior to treatment. A possible mechanism supporting the clinical benefit of nimodipine for SAH patients involves the preferential dilation of small arterioles and subsequent increases in collateral blood flow to ischemic tissues. Nimodipine may protect against or ameliorate the effects of ischemia by blocking the entry of calcium into neurons. Also, by significantly increasing endogenous fibrinolytic activity, nimodipine may act to reduce the incidence of microthrombosis after SAH.\textsuperscript{8,10,13}

What are the pharmacokinetics and bioavailability of Nymalize?

Based on an in vitro comparison with nimodipine capsules, Nymalize was granted a bio-waiver by the FDA, and separate pharmacokinetic studies with Nymalize were not required.

Nimodipine is widely distributed into body tissues and is rapidly and almost completely absorbed following oral administration. Because of extensive first-pass metabolism in the liver, oral bioavailability of nimodipine is low and variable, averaging approximately 13%. The presence of food in the gastrointestinal tract can substantially decrease the extent of oral absorption of nimodipine. Peak concentrations are attained within 1 hour after oral administration of single doses. Clearance of nimodipine may be substantially decreased, and systematic availability of the drug increased, in patients with liver disease.\textsuperscript{10}
Questions & Answers About Nymalize

How effective is Nymalize Oral Solution at improving neurological outcomes and reducing the incidence and severity of ischemic deficits after SAH?

The primary evidence supporting the effectiveness of oral nimodipine comes from four randomized double-blind placebo-controlled trials.\textsuperscript{14-17} The dosing in these trials ranged from 20-30 mg to 90 mg every 4 hours, with the drug given for 21 days in three of the trials and for at least 18 days in the fourth. In two of these trials, with relatively unimpaired SAH patients randomized, nimodipine-treated patients experienced significantly fewer severe deficits due to spasm than placebo patients (1 vs 8 in one trial,\textsuperscript{14} 2 vs 10 in the other\textsuperscript{15}).

In a third trial, the largest of the four with 554 SAH patients with all grades of severity (89% Hunt and Hess grades I to III), nimodipine-treated patients experienced a significant reduction in the overall rate of infarction and severely disabling neurological outcome at 3 months. Cerebral infarcts were experienced by 22% (61/278) of nimodipine-treated patients versus 33% (92/276) of placebo patients, a significant reduction of 34% (95% CI 13% to 50%). Nimodipine treatment also significantly reduced the incidence of poor outcome (death, vegetative state, or severe disability) by 40%, from 33% (91/276) for placebo patients to 20% (55/278) for nimodipine-treated patients.\textsuperscript{16}

In the fourth of the nimodipine trials, which enrolled much sicker patients (Hunt and Hess grades III to V), nimodipine-treated patients experienced a significant reduction in vasospasm-related delayed ischemic deficits, with permanent deficits occurring in 6.9% (5/72) of nimodipine-treated patients versus 26.8% (22/82) of placebo patients (p <0.05).\textsuperscript{17} An outcome characterized as “good recovery” (Glasgow Outcome Scale\textsuperscript{18}) was experienced by 29.2% (21/72) of nimodipine-treated patients versus 9.8% (8/82) of placebo patients (p <0.001).\textsuperscript{17} (The five categories in the Glasgow Outcome Scale are dead, vegetative state, severe disability, moderate disability, and good recovery.\textsuperscript{18})

A further subgroup analysis of outcomes from the third and fourth of these trials demonstrated that treatment with oral nimodipine tends to improve the “good recovery” of SAH patients who have poor neurological status post-ictus, while decreasing the incidence of severe disability and vegetative survival. In this combined subgroup cohort of SAH patients with initial Hunt and Hess grades IV or V, “good recovery” was experienced by 25.3% of nimodipine-treated patients versus 10.9% of placebo patients.\textsuperscript{1}

What are the contraindications for Nymalize?

None are known.
Questions & Answers About Nymalize

What are the labeled warnings and precautions concerning Nymalize?

Hypotension: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked when the warning against intravenous administration is observed. In clinical studies of patients with SAH, about 5% of nimodipine-treated patients compared to 1% of placebo patients had hypotension, and about 1% of nimodipine-treated patients left the study because of this. Blood pressure should be carefully monitored during treatment with nimodipine based on the drug's known pharmacology and the known effects of calcium channel blockers.

Possible increased risk of adverse reactions in patients with cirrhosis: Patients with hepatic cirrhosis have substantially reduced renal clearance, and peak plasma concentrations achieved in these patients may be substantially higher than those in patients with normal hepatic function. Because such patients are at higher risk of adverse reactions, they should have their blood pressure and pulse rate monitored closely and should be given a lower dose.

Possible increased risk of hypotension with strong CYP3A4 inhibitors: See the next section on associated drug interactions.

Possible reduced efficacy with strong CYP3A4 inducers: See the next section on associated drug interactions.

Are there significant drug interactions associated with Nymalize?

Other blood-pressure-lowering drugs: Nymalize may increase the blood-pressure-lowering effect of concomitantly administered antihypertensive drugs (diuretics, beta blockers, angiotensin-converting-enzyme [ACE] inhibitors, alpha-adrenergic blocking agents, other calcium channel blockers, phosphodiesterase type 5 [PDE-5] inhibitors, alpha-methyldopa). Blood pressure should be carefully monitored, and dose adjustment of the blood-pressure-lowering drugs may be necessary.

CYP3A4 inhibitors: Nimodipine is metabolized via the cytochrome P450 3A4 system, and drugs known to inhibit this enzyme system may therefore alter the first-pass metabolism or reduce clearance of nimodipine, leading to increased plasma concentrations of the drug and increased blood-pressure-lowering effect. Concomitant administration of Nymalize with strong CYP3A4 inhibitors (eg, macrolide antibiotics, HIV protease inhibitors, hepatitis C virus protease inhibitors, azole antimycotics) should generally be avoided. When Nymalize is co-administered with any strong, moderate, or weak CYP3A4 inhibitor, blood pressure should be monitored, and if necessary a reduction of the nimodipine dose should be considered.

CYP3A4 inducers: Concomitant use of Nymalize with strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort) should generally be avoided, as the nimodipine plasma concentration and efficacy may be significantly reduced.
Are there significant food interactions associated with Nymalize?

Grapefruit juice inhibits the cytochrome P450 3A4 enzyme system. Administration of dihydropyridine calcium channel antagonists such as nimodipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nimodipine due to a decreased first-pass metabolism or reduced clearance. The blood-pressure-lowering effect may be increased. Ingestion of grapefruit or grapefruit juice is not recommended while taking Nymalize.

What are the most common adverse reactions associated with Nymalize?

Nimodipine is generally well tolerated following oral administration. In clinical studies, adverse reactions were reported for 11.2% (92/823) of SAH patients treated with oral nimodipine. Adverse events were reported by 6.1% (29/479) of placebo patients in these studies. The most frequently reported adverse reaction was decreased blood pressure, occurring in 4.4% of the nimodipine-treated patients.

Besides decreased blood pressure, other adverse events reported by nimodipine-treated patients with a frequency of greater than 1% were edema, diarrhea, rash, headache, gastrointestinal symptoms, nausea, dyspnea, EKG abnormalities, tachycardia, bradycardia, muscle pain or cramping, acne, and depression.

In the clinical studies, adverse events that appeared related to nimodipine use based on increased incidence with higher dose or on a higher rate compared to placebo control included decreased blood pressure and headache — which are known pharmacologic actions of calcium channel blockers.

In the largest of the four randomized double-blind placebo-controlled trials of oral nimodipine, the 17 adverse reactions reported in the 278 nimodipine-treated SAH patients included headache (n = 3), flushing (n = 1), hypertension (n = 1), hypotension (n = 1), jaundice (n = 2), liver function test abnormalities (n = 2), rash (n = 2), and 5 other unspecified events each occurring in one patient. In 8 patients receiving nimodipine and 3 patients receiving placebo, the adverse reactions were sufficiently severe to warrant withdrawal from the trial. Routine hematological and biochemical laboratory data were comparable between the nimodipine-treated and placebo groups.16

SAH is frequently accompanied by alterations in consciousness that may lead to an under-reporting of adverse experiences. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with arteriovenous conduction, but these events were not observed in SAH trials.
How is Nymalize dosed and administered?

The recommended dosage of Nymalize Oral Solution is 20 mL (60 mg) every 4 hours for 21 consecutive days, preferably not less than 1 hour before or 2 hours after meals. Patients with cirrhosis should be given a reduced dosage of 10 mL (30 mg) every 4 hours.

When the patient is unconscious or otherwise unable to swallow, an oral syringe should be used to administer the dose, on the same schedule, through a nasogastric or gastric tube into the stomach. After the enteral administration of Nymalize through a nasogastric or gastric tube, an oral syringe should be refilled with 20 mL of 0.9% saline water solution and used to flush any remaining contents from the tube into the stomach.

Oral nimodipine should not be administered intravenously or by other parenteral routes. If inadvertent intravenous administration does occur, clinically significant hypotension may require cardiovascular support with pressor agents, and specific treatments for calcium channel blocker overdose should also be given promptly. When an oral syringe is used to administer Nymalize through a nasogastric or gastric tube, that syringe should be labeled ORAL USE ONLY.

How does Nymalize taste?

The taste of Nymalize has been described as neutral with a slight sweetness.

Are there specific considerations regarding Nymalize use or dosing in special populations?

Pregnancy, breastfeeding, pediatric patients: As a pregnancy category C drug, based on findings in animal studies, Nymalize should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women to directly assess the effect of Nymalize on human fetuses. It is not known whether the drug is excreted in human milk, but as many drugs are, nursing mothers are advised not to breast feed their babies when taking nimodipine. The safety and effectiveness of nimodipine in pediatric patients have not been established.

Elderly patients: In the absence of definitive clinical study findings, dosing in elderly patients should in general be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
How is Nymalize supplied and stored?

Nymalize Oral Solution is available as a 16 ounce bottle and in a package of twelve 10 mL or 20 mL unit dose cups. Each 10 mL unit dose cup contains 30 mg of nimodipine. Each 20 mL unit dose cup contains 60 mg of nimodipine.

The packaging of Nymalize thus meets the medication-storage provision in the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) medication-management standards, according to which: “Medications stored in patient care areas are in the most ready-to-administer forms commercially available or repackaged by the pharmacy or a licensed repackager.”

Nymalize should be stored at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F), and protected from light. Nymalize should not be refrigerated.

Once opened, the 16 ounce bottle should be resealed and kept at room temperature. The unit dose cups should be discarded after use. The expiration date is printed on each carton, cup, and bottle.

What is the FDA’s recommendation on when to use Nymalize or nimodipine capsules for patients with SAH?

In April of 2014, the FDA released an official communication titled “Determination That NIMOTOP (Nimodipine) Capsules, 30 Milligrams, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness.”

In this communication, the FDA acknowledged that despite ongoing efforts by the FDA and the manufacturers of nimodipine capsules, potentially fatal medication errors due to liquid extraction of nimodipine were still occurring. This was specifically impacting patients who were unconscious and unable to swallow nimodipine capsules.

The FDA acknowledged that Nymalize can “prevent erroneous intravenous administration because it can be used for those patients who are unconscious or unable to swallow and eliminates the need for use of a parenteral syringe, which is the source of the medication errors.”

What is the recommendation of the Institute for Safe Medication Practices on the use of Nymalize?

The ISMP expressed its concerns about the use of capsule extraction in February 2013, when it reported the death of a woman admitted for SAH who was inadvertently administered liquid nimodipine through her central IV line instead of her nasogastric tube.

The ISMP followed up in July 2013 with its recommendation that hospitals currently extracting nimodipine from capsules use Nymalize when a liquid form of nimodipine is needed.
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**Is Nymalize administration included in the Comprehensive Stroke Performance Measurements?**

Yes. Certified Comprehensive Stroke Centers must meet performance measurement requirements, including 8 Joint Commission stroke (STK) measures and 8 comprehensive stroke (CSTK) measures. In 2015, CSTK6 was amended to include Nymalize. CSTK6 assesses whether patients were administered nimodipine within 24 hours of arrival at the hospital (or continued nimodipine treatment if it was initiated at another hospital).\(^{23-25}\)

**How many doses does 1 bottle (or 1 tray of cups) provide a patient?**

A 16 oz bottle supplies one SAH patient 23 (60 mg) doses of liquid nimodipine, which should last the patient 3.8 days. One carton of twelve 60 mg (20 mL) unit dose cups supplies 12 doses of liquid nimodipine, enough to last 2 days. If a patient is on a reduced dosage of 30 mg (10 mL) every 4 hours, a carton of twelve 30 mg (10 mL) unit dose cups will supply the patient with 12 doses of liquid nimodipine, enough to last 2 days.

**References**

1. Nymalize full prescribing information.


