

# **NYMALIZE- nimodipine solution**

## **Azurity Pharmaceuticals, Inc.**

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### **HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use NYMALIZE® safely and effectively. See full prescribing information for NYMALIZE.**

**NYMALIZE (nimodipine) oral solution**  
**Initial U.S. Approval: 1988**

### **INDICATIONS AND USAGE**

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 (i.e., Hunt and Hess Grades I-V). (1)

### **DOSAGE AND ADMINISTRATION**

- Administer only enterally (e.g., oral, nasogastric tube, or gastric tube route). Do not administer intravenously or by other parenteral routes. (2.1)
- Give one hour before a meal **or** two hours after a meal. (2.1)
- Start dosing within 96 hours of the SAH. (2.1)
- Recommended dose is 10 mL (60 mg) every 4 hours for 21 consecutive days. (2.2)
- *Nasogastric or Gastric Tube Administration:* Administer 10 mL (60 mg) every 4 hours with supplied prefilled oral syringe. Refill syringe with 10 mL of 0.9% saline water solution; flush remaining contents from nasogastric or gastric tube into stomach. (2.3)
- *Patients with Cirrhosis:* Reduce dosage to 5 mL (30 mg) every 4 hours. (2.4)

### **DOSAGE FORMS AND STRENGTHS**

Oral solution (6 mg per mL):

- 60 mg per 10 mL in unit-dose prefilled syringe (3)
- 30 mg per 5 mL in unit-dose prefilled syringe (3)
- 60 mg per 10 mL (6 mg/mL) in 8 oz bottle (3)

### **CONTRAINDICATIONS**

None (4)

### **WARNINGS AND PRECAUTIONS**

- *Hypotension:* Monitor blood pressure. (5.1)
- *Patients with Cirrhosis:* Higher risk of adverse reactions. Monitor blood pressure and pulse. (5.2)
- *CYP3A4 Strong Inhibitors:* May significantly increase risk of hypotension. Concomitant use with NYMALIZE should generally be avoided. (5.3)
- *CYP3A4 Strong Inducers:* May significantly reduce efficacy of nimodipine. Concomitant use with NYMALIZE should generally be avoided. (5.4)

### **ADVERSE REACTIONS**

Most common adverse reactions (incidence  $\geq 1\%$  and  $\geq 1\%$  placebo) were hypotension, headache, nausea, and bradycardia. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Azurity Pharmaceuticals, Inc. at 1-800-461-7449 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### **DRUG INTERACTIONS**

- *Anti-Hypertensives:* May increase risk of hypotension. Monitor blood pressure. (7.1)
- *CYP3A4 Moderate and Weak Inhibitors:* May increase risk of hypotension. Monitor blood pressure. Dose reduction of NYMALIZE may be needed. Avoid grapefruit juice. (7.2)
- *CYP3A4 Moderate and Weak Inducers:* May reduce efficacy of NYMALIZE. Dose increase may be needed. (7.3)

### **USE IN SPECIFIC POPULATIONS**

- *Pregnancy:* Based on animal data may cause fetal harm. (8.1)

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## **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 10 mL (60 mg) every 4 hours for 21 consecutive days.

### **2.3 Administration Via Nasogastric or Gastric Tube**

Using the supplied prefilled oral syringe labeled "For Oral Use Only", administer 10 mL (60 mg) every 4 hours into a nasogastric or gastric tube for 21 consecutive days. For each dose, refill the syringe with 10 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 5 mL (30 mg) every 4 hours [see *Warnings and Precautions (5.2)*, *Clinical Pharmacology (12.3)*].

## **3 DOSAGE FORMS AND STRENGTHS**

Oral Solution (6 mg per mL):

- 60 mg per 10 mL, pale yellow solution in unit-dose prefilled syringe
- 30 mg per 5 mL, pale yellow solution in unit-dose prefilled syringe
- 60 mg per 10 mL (6 mg/mL), pale yellow solution in 8 oz bottle

## **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 antimycotics (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)*].

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In clinical trials of nimodipine oral capsules in patients with SAH, eleven percent (92 of 823) of nimodipine-treated patients reported adverse events compared to six percent (29 of 479) of placebo-treated patients. The most common adverse event was decreased blood pressure in 4.4% of nimodipine-treated patients. The events reported with a frequency greater than 1% are displayed in Table 1 by dose.

**Table 1: Adverse Events [n (%)] reported with a**

**frequency > 1% in four clinical trials (Study 1, Study 2, Study 3, and Study 4)**

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

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,  $\alpha$ -adrenergic blockers, PDE5 inhibitors, and  $\alpha$ -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, ameprenavir, 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)].

Moderate and weak inducers of CYP3A4 may also reduce the efficacy of nimodipine. Patients on these should be closely monitored for lack of effectiveness, and a nimodipine dosage increase may be required. Moderate and weak CYP3A4 inducers include, for example: ameprenavir, aprepitant, armodafinil, bosentan, efavirenz, etravirine, Echinacea, modafinil, nafcillin, pioglitazone, prednisone, rufinamide, and vemurafenib.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no adequate data on the developmental risk associated with the use of NYMALIZE in pregnant women. In animal studies, oral administration of nimodipine during pregnancy resulted in adverse effects on development (increased embryofetal mortality, increased incidences of fetal structural abnormalities, decreased fetal growth)

at doses equivalent to (rat) or less than (rabbit) those used clinically [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

## Data

### *Animal Data*

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). The lowest effect dose in rabbits (1 mg/kg/day) is less than the recommended human dose (RHD) of 360 mg/day on a body surface area (mg/m<sup>2</sup>) basis.

Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses in rats at 100 mg/kg/day administered orally throughout organogenesis; this dose is approximately 3 times the RHD on a mg/m<sup>2</sup> basis. In two other studies in rats, nimodipine administered orally at 30 mg/kg/day throughout organogenesis and continued until sacrifice (day 20 of pregnancy or day 21 postpartum) was associated with higher incidences of skeletal variation, stunted fetuses, and stillbirths but no malformations; this dose is similar to the RHD on a mg/m<sup>2</sup> basis.

## **8.2 Lactation**

### Risk Summary

Nimodipine has been detected in human milk. There are no data on the effects of nimodipine on the breastfed infant or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NYMALIZE and any potential adverse effects on the breastfed infant from NYMALIZE or from the underlying maternal condition.

## Data

### *Animal Data*

[<sup>14</sup>C]Nimodipine and its radiolabeled metabolites were secreted in milk of orally dosed lactating rats. The milk concentration of nimodipine and/or metabolites was higher than that in plasma, with a milk/plasma ratio of 0.65 to 4.7.

## **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

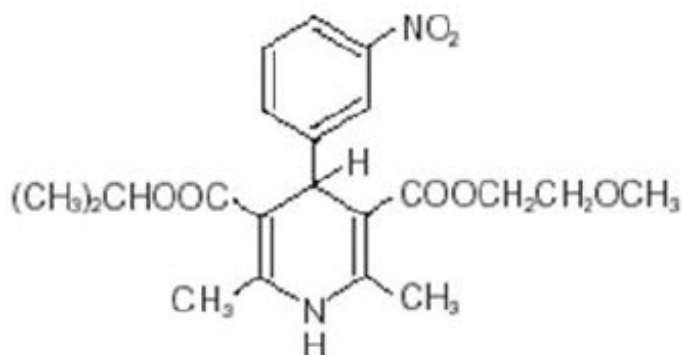
cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy [see *Clinical Pharmacology* (12.3)].

## 10 OVERDOSAGE

There have been no reports of overdose from the oral administration of nimodipine. Symptoms of overdose would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to nimodipine overdose 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  $C_{21}H_{26}N_2O_7$ . The structural formula is:



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

NYMALIZE Oral Solution contains 60 mg of nimodipine per 10 mL. In addition, the oral solution contains the following inactive ingredients: ethanol, glycerin, methylparaben, polyethylene glycol 400.

## 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**

After a single 60 mg oral dose of NYMALIZE, mean (CV%)  $C_{max}$  was 69.9 ng/mL (36.1%),  $AUC_{inf}$  was 151 h·ng/mL (36.0%) and within subject variability (CV%) was 21.7% and 12.4%, respectively. There were no signs of accumulation when nimodipine was given three times a day for seven days.

#### Absorption

In humans, nimodipine was absorbed with a time to maximum concentration ( $T_{max}$ ) ranging from 0.25 to 1.05 hours following oral administration. Because of a high first-pass metabolism, the bioavailability of nimodipine averages 13% after oral administration.

#### *Effect of Food*

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)*].

#### Distribution

Nimodipine is over 95% bound to plasma proteins. The binding was concentration independent over the range of 10 ng/mL to 10 mcg/mL.

#### Elimination

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.

#### *Metabolism*

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 [see *Drug Interactions (7.2, 7.3)*].

#### *Excretion*

Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug.

#### Specific Populations

##### *Patients with Cirrhosis*

The bioavailability of nimodipine is significantly increased in patients with cirrhosis, with  $C_{max}$  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 years) and 24 younger subjects (aged 22-40 years), the observed AUC and  $C_{max}$  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 [less than the recommended dosing regimen] for 6 days). The clinical response to these age-related pharmacokinetic differences, however, was not considered significant [see *Use in Specific Populations (8.5)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### *Carcinogenesis*

In a two-year study in rats, 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/m<sup>2</sup>) 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**

Study	Grade*	Treatment	Patients		
			Number Analyzed	Number of Patients with Any Deficit Due to Spasm	Numbers with Severe Deficit
Study 1	I-III	Nimodipine 20-30 mg every 4 hours	56	13	1
		Placebo	60	16	8 <sup>†</sup>
Study 2	I-III	Nimodipine 60 mg every 4 hours	31	4	2
		Placebo	39	11	10 <sup>†</sup>

\* 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):

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

	Nimodipine	Placebo
Total patients	278	276
Good recovery	199*	169
Moderate disability	24	16
Severe disability	12 <sup>†</sup>	31
Death	43 <sup>‡</sup>	60

\* p = 0.0444 - good and moderate vs severe and dead

† p = 0.001 - severe disability

‡ p = 0.056 - death

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 4: Neurological Ischemic Deficits in Study 4 [Hunt and Hess Grades III-V]**

	Delayed Ischemic Deficits (DID)		Permanent Deficits	
	Nimodipine 90 mg every 4 hours n (%)	Placebo n (%)	Nimodipine 90 mg every 4 hours n (%)	Placebo n (%)
DID Spasm Alone	8 (11)*	25 (31)	5 (7)*	22 (27)
DID Spasm Contributing	18 (25)	21 (26)	16 (22)	17 (21)
DID Without Spasm	7 (10)	8 (10)	6 (8)	7 (9)
No DID	39 (54)	28 (34)	45 (63)	36 (44)

\* p = 0.001, Nimodipine vs 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**

Glasgow Outcome*	Nimodipine (n=87)	Placebo (n=101)
Good Recovery	22 (25.3%)	11 (10.9%)
Moderate Disability	8 (9.2%)	12 (11.9%)
Severe Disability	6 (6.9%)	15 (14.9%)
Vegetative Survival	4 (4.6%)	9 (8.9%)
Death	47 (54.0%)	54 (53.5%)

\* 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 6 mg/mL is a pale yellow solution and is supplied as follows:

- NDC 24338-260-08: 8 oz. bottle (237 mL) 60 mg/10 mL (6 mg/mL)
- NDC 24338-260-12: Carton containing 12 individually wrapped 10 mL packages. Each package contains one 60 mg/10 mL unit-dose prefilled oral syringe with a purple plunger (NDC 24338-260-10).
- NDC 24338-230-12: Carton containing 12 individually wrapped 5 mL packages. Each package contains one 30 mg/5 mL unit-dose prefilled oral syringe with a white plunger (NDC 24338-230-05).

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) [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)*].

Advise patients to notify their healthcare provider if they become pregnant during treatment or plan to become pregnant during therapy [see *Use in Specific Populations (8.1)*].

Advise female patients to notify their physicians if they intend to breastfeed or are breastfeeding an infant [see *Use in Specific Populations (8.2)*].

Manufactured for:  
Azurity Pharmaceuticals, Inc.  
Woburn, MA 01801

Manufactured by:  
Delpharm Montréal Inc.  
Pointe-Claire, QC, Canada  
H9R 1B4

Distributed by Azurity Pharmaceuticals, Inc. Woburn, MA 01801

NYMALIZE is a registered trademark of Azurity Pharmaceuticals, Inc.

NIM-PI-11 3/2023

Patent: <https://azurity.com/patents>

## **PRINCIPAL DISPLAY PANEL - 10 mL Syringe Label**

Mfg. for Azurity Pharmaceuticals, Inc.  
Woburn, MA 01801  
Pkg. by Safecor Health  
Columbus, OH

NDC 2433826010

Store at controlled  
room temperature, USP.  
Protect from light.  
Do not refrigerate.

Nymalize®  
(nimodipine) oral solution

60 mg/10 mL

For Oral Use Only  
Rx Only

Rev. 05/22  
Lot XXXXXXX  
Exp. YYYY-MM-DD

Mfg. for Azurity Pharmaceuticals, Inc.  
Woburn, MA 01801  
Pkg. by Safecor Health  
Columbus, OH



NDC 2433826010

Store at controlled  
room temperature, USP.  
Protect from light.  
Do not refrigerate.

**Nymalize®**   
**(nimodipine) oral solution**

---

**60 mg/10 mL**

**For Oral Use Only**    Rx Only

Rev. 05/22  
Lot XXXXXXX  
Exp. YYYY-MM-DD

**PRINCIPAL DISPLAY PANEL - 10 mL Syringe Package**

10 mL

Nymalize®  
(nimodipine)  
oral solution

60 mg / 10 mL

For Oral Use Only

Recommended Dosage:  
See prescribing information.

Keep out of reach of children  
Package not child resistant

Store between 20°C to 25°C (68°F - 77°F);  
excursions permitted to 15°C to 30°C (59°F - 86°F)  
[see USP Controlled Room Temperature]

Protect from light  
Do not refrigerate

NDC: 24338-260-10

One 10 mL Unit-Dose Oral Syringe

Rx Only

EXP: 2023-05-31

Lot: 22A0047

Mfg For Azurity Pharmaceuticals, Inc. Woburn, MA 01801  
Pkg By Safecor, Columbus, OH 43204

NYM-OW10-S01

REV. 05/22

10 mL

**Nymalize<sup>®</sup>**  
**(nimodipine)**  
**oral solution**  
**60 mg / 10 mL**

**For Oral Use Only**

Recommended Dosage:  
See prescribing information.

**Keep out of reach of children**  
**Package not child resistant**

Store between 20°C to 25°C (68°F - 77°F);  
excursions permitted to 15°C to 30°C (59°F - 86°F)  
[see USP Controlled Room Temperature]

Protect from light  
Do not refrigerate







2433826010

**NDC: 24338-260-10**

**One 10 mL Unit-Dose Oral Syringe**

**Rx Only**

**EXP: 2023-05-31**

**Lot: 22A0047**

Mfg For Azurity Pharmaceuticals, Inc. Woburn, MA 01801

Pkg By Safecor, Columbus, OH 43204

NYM-OW10-S01 REV. 05/22

**PRINCIPAL DISPLAY PANEL - 10 mL Syringe Package Carton**

NDC: 24338-260-12

Rx Only

Nymalize<sup>®</sup>

(nimodipine) oral solution

60 mg/10 mL

Contains 12 Prefilled  
Oral Syringes

For Oral Use Only

Distributed by:

azurity<sup>®</sup>

pharmaceuticals

Woburn, MA 01801

NDC: 24338-260-12

Rx Only

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution

60 mg/10 mL

For Oral Use Only

Contains 12 Prefilled  
Oral Syringes

Distributed by:  
**azurity**  
pharmaceuticals  
Webster, MA 01801

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution  
60 mg/10 mL



NO COATING

NO  
COATING

Distributed by:  
**azurity**  
pharmaceuticals  
Webster, MA 01801

Contains 12 Prefilled Oral Syringes

For Oral Use Only

60 mg/10 mL

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution

Rx Only

NDC: 24338-260-12

NDC: 24338-260-12

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution

60 mg/10 mL

Inactive Ingredients:  
Polyethylene Glycol 400,  
Glycerin, Ethanol, Methylparaben

Recommended Dosage: See prescribing information.

Keep out of reach of children.

Package not child resistant.

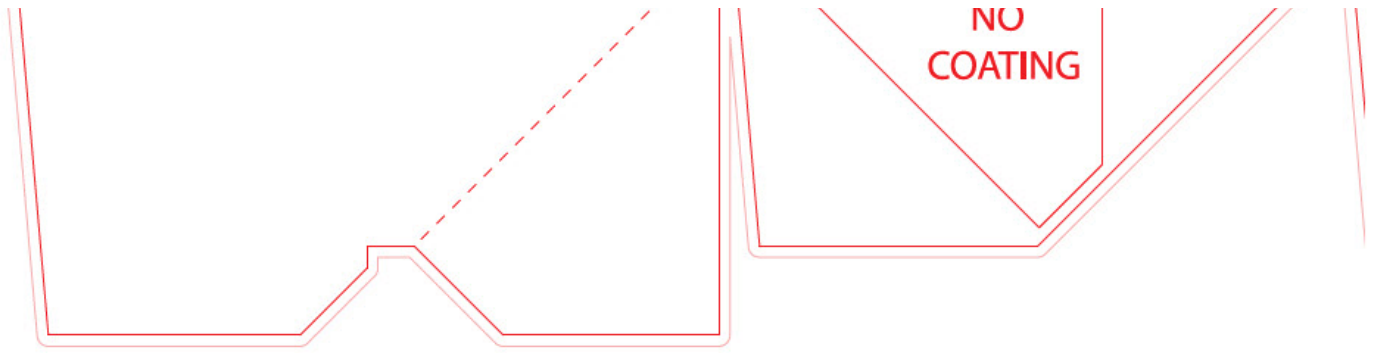
Store between 20°C to 25°C (68°F - 77°F);  
excursions permitted to 15°C to 30°C (59°F - 86°F).  
[see USP Controlled Room Temperature]

Protect from light.  
Do not refrigerate.

NYM-STC10-S01 Rev. 05/22



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## **PRINCIPAL DISPLAY PANEL - 5 mL Syringe Label**

Mfg. for Azurity Pharmaceuticals, Inc.  
Woburn, MA 01801  
Pkg. by Safecor Health  
Columbus, OH

NDC 2433823005

Store at controlled  
room temperature, USP.  
Protect from light.  
Do not refrigerate.

Nymalize<sup>®</sup>  
(nimodipine) oral solution

30 mg/5 mL

For Oral Use Only  
Rx Only

Rev. 05/22  
Lot XXXXXXX  
Exp. YYYY-MM-DD

Mfg. for Azurity Pharmaceuticals, Inc.  
Woburn, MA 01801  
Pkg. by Safecor Health  
Columbus, OH



NDC 2433823005

**Nymalize**<sup>®</sup>   
(nimodipine) oral solution

**30 mg/5 mL**

**For Oral Use Only Rx Only**

Store at controlled  
room temperature, USP.  
Protect from light.  
Do not refrigerate.

Rev. 05/22  
Lot XXXXXXX  
Exp. YYYY-MM-DD

**PRINCIPAL DISPLAY PANEL - 5 mL Syringe Package**

5 mL

Nymalize<sup>®</sup>  
(nimodipine)  
oral solution

30 mg / 5 mL

For Oral Use Only

Recommended Dosage:  
See prescribing information.

Keep out of reach of children  
Package not child resistant

Store between 20°C to 25°C (68°F - 77°F);  
excursions permitted to 15°C to 30°C (59°F - 86°F)  
[see USP Controlled Room Temperature]  
Protect from light  
Do not refrigerate

NDC: 24338-230-05

One 5 mL Unit-Dose Oral Syringe

Rx Only

EXP: 2023-04-30

Lot: 22A0060

Mfg For Azurity Pharmaceuticals, Inc. Woburn, MA 01801

Pkg By Safecor, Columbus, OH 43204

NYM-OW05-S01

REV. 05/22

5 mL

**Nymalize<sup>®</sup>**  
**(nimodipine)**  
**oral solution**  
**30 mg / 5 mL**

**For Oral Use Only**

Recommended Dosage:  
See prescribing information.

**Keep out of reach of children**  
**Package not child resistant**

Store between 20°C to 25°C (68°F - 77°F);  
excursions permitted to 15°C to 30°C (59°F - 86°F)

[see USP Controlled Room Temperature]

Protect from light  
Do not refrigerate





2433823005

**NDC: 24338-230-05**

**One 5 mL Unit-Dose Oral Syringe  
Rx Only**

**EXP: 2023-04-30**

**Lot: 22A0060**

Mfg For Azurity Pharmaceuticals, Inc. Woburn, MA 01801

Pkg By Safecor, Columbus, OH 43204

NYM-OW05-S01

REV. 05/22

**PRINCIPAL DISPLAY PANEL - 5 mL Syringe Package Carton**

NDC: 24338-230-12

Rx Only

Nymalize®  
(nimodipine) oral solution

30 mg/5 mL

Contains 12 Prefilled  
Oral Syringes

For Oral Use Only

Distributed by:  
azurity®  
pharmaceuticals  
Woburn, MA 01801

NDC: 24338-230-12

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution

30 mg/5 mL

For Oral Use Only

Rx Only

Distributed by:  
**azurity**  
Webster, MA 01801

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution

30 mg/5 mL



NO COATING

Contains 12 Prefilled  
Oral Syringes

NO  
COATING

Distributed by:  
**azurity**  
Webster, MA 01801

Contains 12 Prefilled Oral Syringes

For Oral Use Only

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution  
30 mg/5 mL

Rx Only

NDC: 24338-230-12

NDC: 24338-230-12

**Nymalize**<sup>®</sup>  
(nimodipine) oral solution  
30 mg/5 mL

Inactive Ingredients:  
Polyethylene Glycol 400,  
Glycerin, Ethanol, Methylparaben

Recommended Dosage: See prescribing information.

Keep out of reach of children.

Package not child resistant.

Store between 20°C to 25°C (68°F - 77°F);  
excursions permitted to 15°C to 30°C (59°F - 86°F).  
[see USP Controlled Room Temperature]

Protect from light.  
Do not refrigerate.

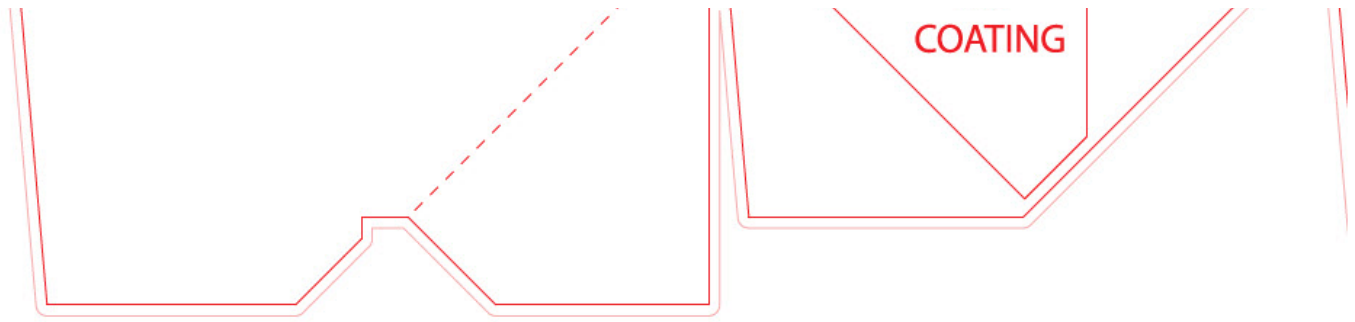
NYM-S1009-S01 Rev. 05/22



5723

NO





## NYMALIZE

nimodipine solution

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:24338-260
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>nimodipine</b> (UNII: 57WA9QZ5WH) (nimodipine - UNII:57WA9QZ5WH)	nimodipine	60 mg in 10 mL

### Inactive Ingredients

Ingredient Name	Strength
<b>polyethylene glycol 400</b> (UNII: B697894SGQ)	
<b>glycerin</b> (UNII: PDC6A3C00X)	
<b>ALCOHOL</b> (UNII: 3K9958V90M)	
<b>methylparaben</b> (UNII: A218C7HI9T)	

### Product Characteristics

<b>Color</b>	YELLOW (pale)	<b>Score</b>	
<b>Shape</b>		<b>Size</b>	
<b>Flavor</b>		<b>Imprint Code</b>	
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:24338-260-12	12 in 1 CARTON	05/04/2020	
1	NDC:24338-260-10	1 in 1 PACKAGE		
1		10 mL in 1 SYRINGE, PLASTIC; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:24338-260-08	237 mL in 1 BOTTLE; Type 0: Not a Combination Product	07/13/2021	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA203340	05/04/2020	

## NYMALIZE

nimodipine solution

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:24338-230
Route of Administration	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>nimodipine</b> (UNII: 57WA9QZ5WH) (nimodipine - UNII:57WA9QZ5WH)	nimodipine	30 mg in 5 mL

### Inactive Ingredients

Ingredient Name	Strength
<b>polyethylene glycol 400</b> (UNII: B697894SGQ)	
<b>glycerin</b> (UNII: PDC6A3C0OX)	
<b>ALCOHOL</b> (UNII: 3K9958V90M)	
<b>methylparaben</b> (UNII: A2I8C7HI9T)	

### Product Characteristics

Color	YELLOW (pale)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:24338-230-12	12 in 1 CARTON	05/04/2020	
1	NDC:24338-230-05	1 in 1 PACKAGE		
1		5 mL in 1 SYRINGE, PLASTIC; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA203340	05/04/2020	

**Labeler** - Azurity Pharmaceuticals, Inc. (117505635)

Revised: 3/2023

Azurity Pharmaceuticals, Inc.