FULL PRESCRIBING INFORMATION

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 orally 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 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) per 4 hours for up to 21 days; refill syringes 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 (8 mL 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 ---

• Administer Monitor blood pressure. (5.1)
• Patients with Cirrhosis: Higher risk of adverse reactions. Monitor blood pressure and pulse. (5.2)
• CVSP44 Strong Inhibitors: May significantly increase risk of hypotension. Concomitant use with NYMALIZE should generally be avoided. (5.3)
• CVSP44 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 >1% and <1%) were hypertension, 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.

--- DRUG INTERACTIONS ---

• Anti-hypertensives: May increase risk of hypotension. Monitor blood pressure. (7.1)
• CVSP44 Moderate and Weak Inhibitors: May increase risk of hypotension. Monitor blood pressure. Dose reduction of NYMALIZE may be needed. Avoid grapefruit juice. (7.2)
• CVSP44 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)

See 17 for PATIENT COUNSELING INFORMATION.

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* Sections or subsections omitted from the full prescribing information are not listed.

Additional information:

--- ADVERSE REACTIONS ---

Table 1: Adverse Events (% of Patients) with Nimodipine Compared to Placebo NYMALIZE 

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Placebo (n=479)</th>
<th>0.35 mg/kg</th>
<th>30 mg</th>
<th>60 mg</th>
<th>90 mg</th>
<th>120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n=82)</td>
<td>(n=71)</td>
<td>(n=49)</td>
<td>(n=72)</td>
<td>(n=57)</td>
<td>(n=6)</td>
</tr>
<tr>
<td>Decreased Blood Pressure</td>
<td>8 (1.2)</td>
<td>1 (1.2)</td>
<td>0</td>
<td>19 (3.8)</td>
<td>14 (8.1)</td>
<td>5 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Ectopia</td>
<td>3 (0.6)</td>
<td>0</td>
<td>0</td>
<td>2 (0.4)</td>
<td>2 (0.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (0.6)</td>
<td>0</td>
<td>3</td>
<td>4 (2.0)</td>
<td>1 (0.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3 (0.6)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3 (0.6)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1</td>
<td>1 (0.6)</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (0.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1 (0.2)</td>
<td>1 (0.6)</td>
<td>0</td>
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<tr>
<td>As reported to the</td>
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</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.

--- 7.2 CYP3A4 Inducers ---

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, concomitant administration of NYMALIZE with 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, and
- nefazodone with nimodipine should generally be avoided because of a risk of significant hypotension (see Drug Interactions (7.3)).

--- 5.4 Possible Reduced Efficacy with Strong CYP3A4 Inducers ---

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 (7.3)).

--- 5.6 Possible Reduced Efficacy with Strong CYP3A4 Inducers ---

Concomitant use of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, 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)).

--- 7.3 CYP3A4 Inducers ---

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 reduced nimodipine dose may be necessary. Moderate and weak CYP3A4 inhibitors include azafruzan, ambenepvir, amiodarone, aripiprazole, azithromycin, benzodiazepines, cilostamide, cilostazone, conivaptan, delavirdine, indinavir, nefazodone, ritonavir, saquinavir, telaprevir, tezosil, and venlafaxine.

--- 8 USE IN SPECIFIC POPULATIONS ---

<table>
<thead>
<tr>
<th>Use</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1 Pregnancy</td>
<td>Risk Summary</td>
</tr>
</tbody>
</table>

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 (reduction in body weight, weight gain, and skeletal development) and an increase in fetal structural abnormalities, decreased fetal growth at doses equivalent to (or less than) 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.
**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 mg/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.

**Special Populations**

**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-center group involving 24 elderly subjects (aged 59-79 years) and 24 younger subjects (aged 22-40 years), 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 [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 adrenocarcinoma 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 500-775 mg/kg/day) was associated with an increased mortality rate.

Mutagenesis

Mutagenicity studies, including the Ames, micronucleus, and dominant lethal assays, were negative in all test systems.

Impairment of Fertility

Nimodipine did not impair the fertility and general reproductive performance of male and female rats following oral dosages 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**

**14.1 General Mechanism of Action**

Nimodipine is a dicyclohexylamine calcium channel blocker. The contractile processes of smooth muscle cells depend on calcium ions, which enter these cells during depolarization as slow ionic transmembrane currents. Nimodipine inhibits calcium ion transfer into these cells and thus inhibits contractile processes of smooth muscle cells. 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 mg/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 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%) Cmax was 69.9 mg/mL (36.1%), AUC0→τ was 151 h·mg/L (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 (Tmax) 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.

**15.4 Delayed Ischemic Deficits (DID)**

**15.5 Permanent Deficits**

**15.6 Good Recovery**

Good recovery was defined as spasm related or not but there was a significant reduction in the number of patients with DID due to spasm contributing.

**15.7 Moderate Disability**

**15.8 Severe Disability**

**15.9 Death**

*p = 0.045, Nimodipine vs placebo

A dose-ranging study comparing 30 mg, 60 mg, and 90 mg doses found a generally linear 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: 60 x 0.25 mL bottles (60 mg/0.1 mL) and 20 x 0.5 mL bottles (20 mg/0.1 mL).

**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 (7.2)].

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: 

Woburn, MA 01801

Manufactured by: 

DePuy Manufacturing Inc.

Pentre-Clare, UK, Canada H1R 1B4

Patent: https://azurity.com/patents

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