

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 203340S011

Name: Nymalize (nimodipine) oral solution,
60 mg/20 mL

Sponsor: Arbor Pharmaceuticals, LLC

Approval Date: June 06, 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

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NDA203340Orig1s011
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA203340Orig1s011

APPROVAL LETTER



NDA 203340 /S-011

APPROVAL LETTER

Arbor Pharmaceuticals, LLC
Attention: Justin Kilby
Senior Manager, Regulatory Affairs
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

Dear Mr. Kilby:

Please refer to your supplemental new drug application (sNDA) dated December 13, 2019, received December 13, 2019, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nymalize (nimodipine) oral solution, 60 mg/20 mL.

We acknowledge receipt of your amendments dated January 10, 2020, February 26, 2020, March 19, 2020, March 20, 2020, March 27, 2020, March 31, 2020, and April 2, 2020.

The December 13, 2019, submission constituted a complete response to our August 2, 2019, action letter.

This Prior Approval sNDA provides for:

1. Reformulation of Nymalize oral solution to provide a 6 mg/mL concentration of nimodipine.
2. Assignment of a shelf life of 12 months at room-temperature storage for the 6 mg/mL oral solution in pre-filled syringes.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling agreed upon on March 31, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labeling for approved NDA 203340/ S-011.**” Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁶

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Vandna Kishore, Regulatory Project Manager, at Vandna.Kishore@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁶ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER
04/08/2020 05:08:43 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA203340Orig1s011

LABELING

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 USE

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)

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 Arbor Pharmaceuticals, LLC at 1-866-516-4950 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)
- 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)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2020

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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 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

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)*].

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, α -adrenergic blockers, PDE5 inhibitors, and α -methyl dopa. 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/dalforpristin, 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: amprenavir, 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/m²) 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/m² 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/m² 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

[¹⁴C]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

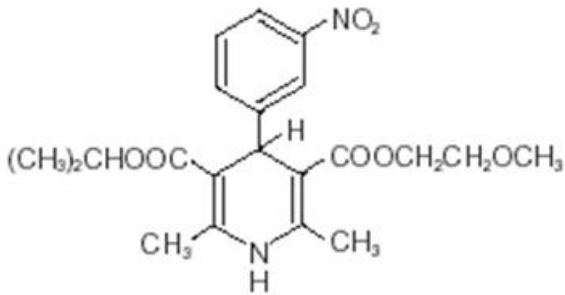
Clinical studies of nimodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they had a different clinical response than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In 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 C₂₁H₂₆N₂O₇. 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/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

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**
Study 2	I-III	Nimodipine 60 mg every 4 hours	31	4	2
		Placebo	39	11	10**

*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**	31
Death	43***	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 24338-260-12: 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:



Arbor Pharmaceuticals, LLC
Atlanta, GA 30328

Manufactured by:

Importfab
Pointe-Claire, QC, Canada
H9R 1C9

Distributed by Arbor Pharmaceuticals, LLC, Atlanta, GA 30328

NYMALIZE is a registered trademark of Arbor Pharmaceuticals, LLC

© 2020 Arbor Pharmaceuticals, LLC

NIM-PI-08

Contains 12 Prefilled Oral Syringes
Distributed by:
Arbor
Pharmaceuticals, LLC
Atlanta, GA 30328

Nymalize®
(nimodipine) oral solution

NEW CONCENTRATION

30 mg/5 mL

For Oral Use Only

NDC: 24338-230-12
Rx Only

NDC: 24338-230-12

Nymalize®
(nimodipine) oral solution

30 mg/5 mL

NEW CONCENTRATION

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-STC05-S00 Rev. 03/20

NDC: 24338-230-12

NEW CONCENTRATION

Nymalize®
(nimodipine) oral solution

30 mg/5 mL

For Oral Use Only

Rx Only

Contains 12 Prefilled
Oral Syringes

Distributed by:
Arbor
Pharmaceuticals, LLC
Atlanta, GA 30328

Nymalize®
(nimodipine) oral solution

30 mg/5 mL

NEW CONCENTRATION

3
24338 23012 1

©2020 Arbor Pharmaceuticals, LLC



GTIN: 00000000000000
SN: (00)000000000000
EXP: 00000000
LOT: 000000

Contains 12 Prefilled Oral Syringes
Distributed by:
Arbor
Pharmaceuticals, LLC
Atlanta, GA 30328

For Oral Use Only

60 mg/10 mL

Nymalize®
(nimodipine) oral solution

NEW CONCENTRATION

Rx Only
NDC: 24338-260-12

NDC: 24338-260-12

Nymalize®
(nimodipine) oral solution
60 mg/10 mL

NEW CONCENTRATION

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-S00 Rev. 03/20

NDC: 24338-260-12

NEW CONCENTRATION

Nymalize®
(nimodipine) oral solution

60 mg/10 mL

For Oral Use Only

Rx Only

Contains 12 Prefilled
Oral Syringes

Distributed by:
Arbor
Pharmaceuticals, LLC
Atlanta, GA 30328

Nymalize®
(nimodipine) oral solution
60 mg/10 mL

NEW CONCENTRATION



©2020 Arbor Pharmaceuticals, LLC



GTIN: 00000000000000
SN: 0000000000000000
EXP: 00000000
LOT: 000000

Mfg. for Arbor Pharmaceuticals, LLC
Atlanta, GA 30328
Pkg. by Safecor Health
Columbus, OH

NEW CONCENTRATION

Nymalize[®] 
(nimodipine) oral solution

30 mg/5 mL

For Oral Use Only Rx Only

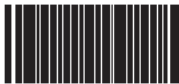


NDC 2433823005

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

Rev. 03/20
Lot XXXXXXXXXX
Exp. YYYY-MM-DD

Mfg. for Arbor Pharmaceuticals, LLC
Atlanta, GA 30328
Pkg. by Safecor Health
Columbus, OH



NDC 2433826010

NEW CONCENTRATION

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. 03/20
Lot XXXXXXXXXX
Exp. YYYY-MM-DD

NEW CONCENTRATION

5 mL

Nymalize[®]
(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: YYYY-MM-DD Lot # 20XXXX

Mfg For Arbor[®] Pharmaceuticals LLC, Atlanta, GA 30328
Pkg By Safecor, Columbus, OH 43204

NEW CONCENTRATION

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



2433826010

NDC: 24338-260-10

One 10 mL Unit-Dose Oral Syringe

Rx Only

EXP: YYYY-MM-DD Lot # 20XXXX

Mfg For Arbor[®] Pharmaceuticals LLC, Atlanta, GA 30328
Pkg By Safecor, Columbus, OH 43204

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA203340Orig1s011

LABELING REVIEW(S)

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 11, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 203340/S-011
Product Name and Strength:	Nymalize (nimodipine) oral solution, 30 mg/5 mL and 60 mg/10 mL (proposed)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Arbor Pharmaceuticals, LLC (Arbor)
FDA Received Date:	December 13, 2019, January 10, 2020, February 26, 2020
OSE RCM #:	2019-810-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

Arbor Pharmaceuticals, LLC submitted a Prior Approval Supplement (PAS), NDA 203340/S-011, for Nymalize (nimodipine) oral solution proposing to:

- change the currently approved formulation (b) (4) nimodipine,
- change the currently approved concentration from 3 mg/mL to 6 mg/mL, and
- replace the currently approved unit-dose cup packaging configurations with a new pre-filled oral syringe packaging configuration.

Subsequently, the Division of Neurology 2 (DN 2) requested that we review the proposed Nymalize oral syringe container labels, carton labeling, overwrap labeling, and prescribing information for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 203340 was approved on May 10, 2013 as a 505(b)(2) and the listed drug product is Nimotop, NDA 018869. On April 5, 2019, Arbor submitted supplement 011. However, a Complete Response Letter (CRL) was issued on August 2, 2019 citing drug substance and product quality deficiencies. We provided additional comments within the CRL, which are documented in our previous review of the originally submitted PAS^a. Therefore, Arbor resubmitted NDA 203340/S-011 on December 13, 2019.

3 MATERIALS REVIEWED

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other – Use Related Risk Analysis	E
Labels and Labeling	F

N/A=not applicable for this review


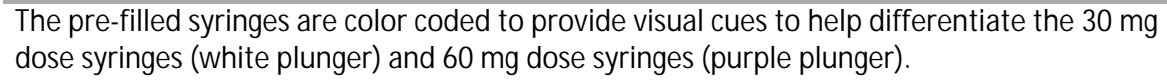
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

^a Little, C. Nymalize (nimodipine) Label Labeling Packaging Review (NDA 203340/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 24. RCM No.: 2019-810.

4 ASSESSMENT OF UPDATED URRA

Based on our additional comments within the CRL regarding potential prescribing errors, Arbor updated their use-related risk analysis (URRA) to include consideration of the risk of potential errors occurring during the prescribing phase of the medication use process.

In the revised URRA (See Appendix E), Arbor identified potential prescribing error scenarios associated with the change in concentration from 3 mg/mL to 6 mg/mL. According to the URRA, the risk associated with potential prescribing errors is wrong dose, which could result in hypotension (overdose) or therapeutic failure (underdose). We note, the risk of wrong dose medication errors exists with the current strengths and is not unique to the change in concentration. Furthermore, Arbor proposes several mitigation strategies (See Appendix E) to further reduce the risk for wrong dose medication errors, including:

- The current concentration (3 mg/mL) will no longer be marketed.
- Existing unit dose cups will be replaced with pre-filled unit dose syringes (that is, 30 mg/5 mL and 60 mg/10 mL) eliminating the need to draw up and measure the correct dose.
- Discontinuation of commercial distribution of the 16 oz. bottle packaging configuration.
-  (b) (4)
- 
- The pre-filled syringes are color coded to provide visual cues to help differentiate the 30 mg dose syringes (white plunger) and 60 mg dose syringes (purple plunger).
- Multi-channel education program/communication process (for example, Dear Healthcare Provider Letter)
- The pre-filled oral syringe container labels, overwrap labeling, and carton labeling will have the statement "New Concentration" on the principal display panel for a period of 6-months.

Considering the totality of Arbor's risk mitigation strategies, we find the residual risk to be mitigated to an acceptable level.

5 LABELS AND LABELING FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted container labels, carton labeling, overwrap labeling and prescribing information, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The term (b) (4), is utilized.	The meaning/definition of (b) (4) - (b) (4) is unclear.	Consider replacing the term (b) (4) with 'unit-dose', if appropriate.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage statement in the PI is inconsistent compared to storage statement on the carton and overwrap labeling and container labels.	May contribute to wrong storage medication errors.	We recommend the storage statement in the PI and on the container labels and carton and overwrap labeling align. We defer to CMC to define the appropriate storage statement.


Table 3. Identified Issues and Recommendations for Arbor Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General			
1.	The statement "NEW CONCENTRATION" lacks prominence. The font color and box color of the statement is similar to other information on the labels and labeling.	May pose risk of this important information being overlooked.	We recommend you revise the statement "NEW CONCENTRATION" to be displayed in bold-face red font and contained within a red box similar to: 
2.	The usual dose statement can be improved.	Not in alignment with language in the Prescribing Information.	Revise the usual dose statement from "Usual Dose: see package insert for complete dosage instructions." to read: "Recommended Dosage: See prescribing information."
3.	The format for the expiration date is not	We are unable to assess the expiration date format from a	Identify the expiration date format you intend to use. FDA

Table 3. Identified Issues and Recommendations for Arbor Pharmaceuticals, LLC (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	defined.	medication safety perspective (for example, may increase the risk for deteriorated drug medication errors).	recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY- MMM- DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY- MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
4.	The proprietary name and the strengths do not appear in their own unique color. The color of the proprietary name (purple) overlaps with the color utilized to highlight the 60 mg/mL strength.	The use of the same purple color font for the proprietary name and one of the product's strengths minimizes the difference between the strengths, which may lead to wrong dose medication errors.	Revise the font color of the proprietary name (purple color) or revise the color scheme of the 60 mg/10 mL strength (purple color), so that either the strength or the proprietary name appears in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
Carton Labeling			
1.	Product identifiers that are required under the Drug Supply Chain Security Act (DSCSA) are not present.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/group

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Nymalize that Arbor Pharmaceuticals, LLC submitted on December 13, 2019.

Table 4. Relevant Product Information for Nymalize	
Initial Approval Date	May 10, 2013
Active Ingredient	nimodipine
Indication	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).
Route of Administration	Enteral (e.g., oral, nasogastric tube, or gastric tube route)
Dosage Form	oral solution
Strength	Current: 30 mg/10 mL and 60 mg/20 mL (3 mg/mL) Proposed: 30 mg/5 mL and 60 mg/10 mL (6 mg/mL)
Dose and Frequency	Current: 20 mL (60 mg) every 4 hours for 21 consecutive days Proposed: 10 mL (60 mg) every 4 hours for 21 consecutive days
How Supplied	<p>Current</p> <ul style="list-style-type: none"> • 16 oz. bottle (473 mL) • Carton containing 12 individually wrapped 20 mL packages. Each package contains one 60 mg/20 mL unit-dose cup and one oral syringe. • Carton containing 12 individually wrapped 10 mL packages. Each package contains one 30 mg/10 mL unit-dose cup and one oral syringe. <p>Proposed</p> <ul style="list-style-type: none"> • Carton containing 12 individually wrapped 10 mL packages. Each package contains one 60 mg/10 mL pre-filled oral syringe with a purple plunger. • Carton containing 12 individually wrapped 5 mL packages. Each package contains one 30 mg/5 mL pre-filled oral syringe with a white plunger.
Storage	Store at 25°C (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.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 1, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms Nymalize and NDA 203340. Our search identified two previous reviews, and we confirmed that our previous recommendations were implemented. The results of our last search can be found in Appendix B of OSE Review #2019-810^a.

On March 3, 2020, we conducted a gap search to identify any reviews finalized since our last search. Our search did not identify any reviews.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
03/11/2020 07:22:00 AM

BRIANA B RIDER
03/11/2020 09:52:03 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA203340Orig1s011

SUMMARY REVIEW(S)

Summary Review

Date	April 8, 2020
From	Heather Fitter, M.D. Nick Kozauer, M.D.
Subject	Summary Review
NDA # and Supplement#	203340/ S-011
Applicant	Arbor Pharmaceuticals
Date of Submission	December 13, 2019
PDUFA Goal Date	April 13, 2020
Proprietary Name	Nymalize
Established or Proper Name	Nimodipine
Dosage Form	Oral solution 30 mg/5 mL and 60 mg/10mL
Route of Administration	Oral
Recommended Proposed Indication/Population	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)
Recommended Proposed Dosing Regimen(s)	60 mg (10 mL) every 4 hours for 21 consecutive days
Recommendation on Regulatory Action	<i>Approval</i>

1. Introduction/Background

Nymalize (nimodipine oral solution) is a dihydropyridine calcium channel blocker that was approved in 2013 for the treatment of aneurysmal SAH at a strength of 60 mg/20 mL. The applicant submitted this resubmission in response to a Complete Response Letter (CRL) received April 5, 2019, for an Office of Product Quality (OPQ)-managed prior approval supplement (PAS) that proposed the addition of a 6 mg/mL formulation to the existing 3 mg/mL formulation. The Complete Response (CR) action was taken on that supplement because of an inadequate drug master file (DMF) for the drug substance (DS), lack of data to support a biowaiver for the new strength, (b) (4)

(b) (4) The current application has attempted to address those deficiencies and again proposes marketing of a Nymalize formulation of 6 mg/mL to replace the formulation currently marketed (3 mg/mL). The applicant has also included in vivo pharmacokinetic (PK) data in this resubmission; therefore, this submission was managed by the Office of New Drugs (OND), as opposed to OPQ.

2. Nonclinical Pharmacology/Toxicology

N/A

3. Product Quality

Dr. Rohit Kolhatkar was the primary product quality reviewer and Dr. David Lewis served as the secondary reviewer. Dr. Kolhatkar reports that the changes in the formulation proposed in this application include increasing the concentration of nimodipine (API) from 3 mg/mL to 6 mg/mL, (b) (4)

Dr. Kolhatkar reports that the manufacturing process (b) (4)

(b) (4) In addition, the applicant provided stability data for up to 12 months at long term stability conditions that support the proposed shelf-life of 12 months.

Dr. Yingzi Wang from the Division of Life Cycle-API was asked to review DMF (b) (4) (nimodipine) and he concludes that the DMF is adequate. Both the drug product (DP) manufacturing facility and the DP packaging facility received an approval recommendation by the Office of Process and Facilities (OPF). (b) (4)

(b) (4) The applicant fulfilled the Division's request to add these facilities to the application. OPF recommended approval for these (b) (4) facilities.

Drs. Kolhatkar and Lewis recommend approval for this supplement.

4. Clinical Pharmacology

Dr. Jagan Parepally was the primary clinical pharmacology reviewer for this application, and Dr. Angela Men was the team leader. Dr. Parepally reviewed the pivotal bioequivalence (BE) study (AR35.001). This bioequivalence study was conducted because it was determined during review of the previous supplement that the requested biowaiver was not supported and a BE study was needed to support marketing of the new formulation. This study was a single-dose, two treatment, two-way crossover (Part 1) and single dose, two treatment, four-period, full-replicate (Part 2) BE study of two different formulations (6 mg/mL vs. 3 mg/mL) of Nymalize in healthy adults under fasted conditions.

An inspection was requested for the BE study, but since the study sites were recently inspected, the Office of Scientific Investigations and Surveillance (OSIS) determined that it was not necessary.

Results

In Part 1, the 90% confidence interval for comparing the maximum and total exposure to nimodipine based on $\ln(C_{\max})$, $\ln(AUC_{\text{last}})$, and $\ln(AUC_{0-\text{inf}})$ were not within the 80% and

125% limits. The sample size was not adequate ($n=6$) based on the variability in PK parameters to draw meaningful conclusions from Part 1. In Part 2, the 90% confidence interval for comparing the maximum and total exposure to nimodipine, based on $\ln(C_{\max})$, $\ln(AUC_{\text{last}})$, and $\ln(AUC_{0-\text{inf}})$ did fall within the 80% and 125% limits.

Dr. Parepally concludes that the two Nymalize formulations compared in this study are bioequivalent.

5. Clinical Microbiology

N/A

6. Clinical/Statistical- Efficacy

No efficacy evaluations were included in this application.

7. Safety

Dr. Lawrence Rodichok conducted the clinical safety review which included safety data from the BE study described in Section 4 of this review.

That study was an open-label, randomized, two-part study in 30 healthy adult subjects. All subjects were dosed after an overnight fast of 10 hours, and each study treatment administration was separated by a washout period of at least 3 days.

In Part 1, six subjects received a single dose of each treatment in a randomized fashion, one treatment in each of the two study periods. All 6 subjects received 1 full dose of Nymalize, 60 mg/10 mL (formulation 1; 6 mg/mL) and 1 full dose of Nymalize, 60 mg/20 mL (formulation 2; 3 mg/mL), for a total exposure of 120 mg of nimodipine.

In Part 2, twenty four subjects received a single dose of each treatment in a randomized fashion in periods 1 and 2; the treatments were then repeated using the same sequence during periods 3 and 4. All 24 subjects received 2 full doses of Nymalize, 60 mg/10 mL (formulation 1) and 2 full doses of Nymalize, 60 mg/20 mL (formulation 2), for a total exposure of 240 mg of nimodipine. All patients enrolled completed the study.

Dr. Rodichok pooled the safety data from both parts of this study. Dr. Rodichok reports that there were no deaths, serious adverse events, or adverse events that resulted in discontinuation of investigational treatment. In addition, he reports that there were no differences in treatment emergent adverse events, by formulation, including adverse events of special interest related to hypotension (e.g., dizziness and flushing). There were no clinically significant differences in the change in blood pressure or pulse between the two formulation.

Dr. Rodichok recommends approval of this application.

8. Other Relevant Regulatory Issues

Division of Medical Error Prevention and Analysis (DMEPA)

Dr. Chad Morris was the DMEPA safety reviewer, and Dr. Briana Rider served as the team leader for the review of the labeling. DMEPA's review of the proposed packaging and labeling identified several areas of vulnerability that could lead to medications errors; however, these concerns were addressed by the applicant and DMEPA recommends approval of this application.

9. Pediatrics

This supplement does not trigger the Pediatric Research Equity Act (PREA) because it does not include a new indication, molecular entity, dosage form, dosing regimen, or route of administration.

10. Labeling

Agreement was reached with the applicant on labeling.

11. Recommendations/Risk-Benefit Assessment

An approval action should be taken for this supplement.

12. Postmarketing Recommendations

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HEATHER D FITTER
04/08/2020 02:50:22 PM

NICHOLAS A KOZAUER
04/08/2020 03:15:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA203340Orig1s011

CHEMISTRY REVIEW(S)

**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls**

1. NDA Supplement Number: NDA 203340 /S-011-RESUB-414

2. Submission(s) Being Reviewed:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Resubmission	PAS	12/13/2019	12/13/2019	12/16/2019	4/13/2020	3/4/2020
Amendments for IR		1/10/2020 2/26/2020 3/19/2020 3/20/2020 3/27/2020				3/4/2020 3/4/2020 3/30/2020 3/30/2020 3/30/2020

3. Provides For:

1. Reformulation of Nymalize oral solution to provide the same 60 mg of dose of nimodipine in a reduced dosing of 10 mL of solution (6 mg/mL) instead of 20 mL of solution (3 mg/mL).
2. Revision to the container closure system to include new 10 mL and 20 mL polypropylene unit-dose oral syringe with (b) (4) plunger (b) (4).

4. Review 1:

5. Clinical Review Division: Division of Neurology Products (DNP)

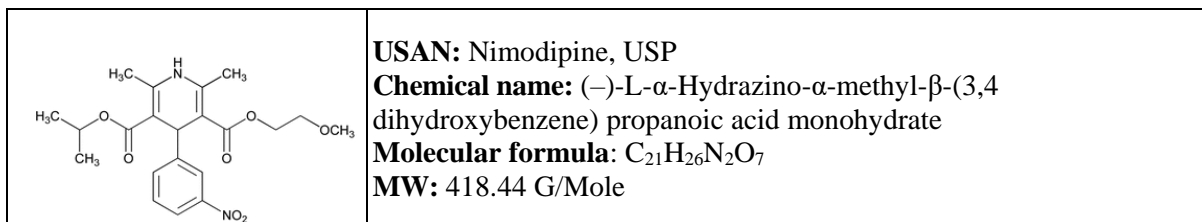
6. Name and Address of Applicant:

Arbor Pharmaceuticals, LLC
6 Concourse Parkway
Suite 1800
Atlanta, GA 30328

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Nymalize® (nimodipine)	Solution	30 mg/5 mL 60 mg/10 mL	Oral	Rx	Yes Orphan Designation Number # 11-3386

8. Chemical Name and Structure of Drug Substance:



9. **Indication:** treatment of subarchnoid hemorrhage

10. Supporting/Relating Documents:

1. REGIONAL

A. Labeling (1.14)

2. DRUG PRODUCT (3.2.P)

A. Control of Drug Product (3.2.P.5): Specifications (3.2.P.5.1)

B. Stability (3.2.P.8): Stability Summary and Conclusion (3.2.P.8.1), Post-approval stability protocol and stability commitment (3.2.P.8.2), Stability Data (3.2.P.8.3)

11. Consults:

Consults	Recommendation	Date	Reviewer
Division of Life Cycle-API DMF# (b) (4) (nimodipine)	Adequate	3/12/2019	Dr. Yingzi Wang
Office of Process and Facilities	Approve	12/20/2019	Raeann Wu
Biopharm	NAI	7/29/2019	Dr. Okpo Eradiri
Pharm-Tox	NAI		Dr. Richard Siarey

12. Executive Summary:

This **resubmission** of PAS supplement **managed by OND** provides for

1. Reformulation of Nymalize oral solution to provide the same 60 mg of dose of nimodipine in a reduced dosing of 10 mL of solution (6 mg/mL) instead of 20 mL of solution (3 mg/mL).
2. Revision to the container closure system to include new 10 mL and 20 mL polypropylene unit-dose oral syringe with (b) (4) plunger (b) (4)

The proposed changes are considered to have a substantial potential to have an adverse effect on the drug product quality per Changes to an Approved NDA and ANDA (CANA) guidance section V (Change in formulation).

The new formulation strength (6 mg/mL) will replace the currently marketed strength (3 mg/mL).

The original submission received complete response (CR) action because of inadequate DMF for the drug substance (DS), lack of data to support biowaiver for new strength, and concerns related to the [REDACTED] (b) (4)
The original submission [REDACTED] (b) (4)

[REDACTED] (b) (4)

This resubmission contains clinical PK data. Therefore, this is managed by OND. Original submission was managed by OPQ.

Division of Life Cycle-API was consulted for the review of DMF# [REDACTED] (b) (4) (nimodipine) and LC-API reviewer, Dr. Wang recommended that the DMF is adequate. [REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4). The applicant was asked to add these facilities in the form 356 h and module 3. The applicant updated required documents in an amendment dated 3/27/2020. These [REDACTED] (b) (4) facilities were recommended for approval by Office of Process and Facilities (OPF).

The changes in the formulation include increasing the concentration of nimodipine (API) (3 mg/mL to 6 mg/mL), [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4) This could affect bioavailability. The Division of Biopharmaceutics was consulted during the first cycle of the review, and Biopharmaceutics reviewer, Dr. Okpo Eradiri recommended the supplement for complete response noting that the biowaiver request for the proposed formulation is not acceptable. The applicant addressed this issue by conducting bioequivalence study. ***This resubmission includes results from the Bioequivalence study that will be assessed by OCP reviewer; therefore, Dr. Okpo Eradiri from the Division of Biopharmaceutics indicated that biopharmaceutics reviewer will not be assigned for this resubmission.***

[REDACTED] (b) (4)

[REDACTED] (b) (4) The limit is acceptable as per ICH Q3B. Pharm-Tox consult is not required since the proposed limit is below the qualification threshold. [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4) **The proposed new specifications are acceptable.**

The supplement proposes a change in the CCS to add 10-mL and 20 mL pre-filled syringes. Original submission provided the stability data for three batches for up to 3 months. The data revealed [REDACTED] (b) (4)

[REDACTED] (b) (4) Therefore, the CR letter asked for the data for up to 6 months. **In response, the applicant provided the stability data for up to 12 months at long-term stability conditions that supports the proposed shelf-life of 12 months.**

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4) *facilities were approval by OPF during original submission and they remain approved as per OPF recommendation for this resubmission.* [REDACTED] (b) (4) *facilities found through DMF review were also recommended for approval by OPF.*

Updates are made in the Carton and Container labels and Package Insert due to the change in the strength of the DP and change in the CCS. A few deficiencies were noted that are adequately addressed by the applicant. **The labels are acceptable from CMC perspective.**

The introduction of the proposed concentration into the marketplace would increase the potential for dosing errors. *Division of Medication Error Prevention and Analysis was consulted during the review of the original submission. However, since the resubmission is managed by OND, the consult for DMEPA was originated from OND and will be assessed by OND.*

13. Conclusions & Recommendations:

This supplement is recommended for approval from CMC standpoint.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Rohit Kolhatkar, CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

David Lewis, Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC ASSESSMENT

I BACKGROUND INFORMATION

NDA 203340 for Nymalize® (nimodipine) Solution was approved on 05/10/2013. The Drug Product (DP) Nymalize solution is approved for the strength of 60 mg/20 mL. The DP composition as obtained from the original NDA is provided below

Table 1: Quantitative Composition for Nimodipine Oral Solution

Ingredients	Function	Quality Standard	Amount (grams) per 20mL	Weight/ 100L Volume	IIG Level
Polyethylene glycol 400					(b) (4)
Nimodipine	Active	USP	0.06		(b) (4)
Ethyl alcohol (b) (4)					(b) (4)
Methylparaben (b) (4)					
Glycerin (b) (4)					

The container closure system (CCS) as approved through original NDA is described below

- (b) (4) 16 ounce (500 mL) round, brown, high density polyethylene (HDPE) bottles with white polypropylene (b) (4) child-resistant caps with (b) (4) seal foil liners.
- 25 mL HDPE unit-dose cups with (b) (4) lidding described as (b) (4) sealing.

In the original submission of this supplement the sponsor proposed reformulation and updates to the CCS. **The original submission received complete response action because of inadequate DMF for the drug substance, lack of data to support biowaiver for new strength, and concerns related to the** (b) (4)

Refer to the review for the first cycle submission by Dr. Kolhatkar dated 8/2/2019.

II PROPOSED CHANGES

This resubmission of the PAS supplement provides for

1. Reformulation of Nymalize oral solution to provide the same 60 mg of dose of nimodipine in a reduced dosing of 10 mL of solution (6 mg/mL) instead of 20 mL of solution (3 mg/mL).
2. Revision to the container closure system to include new 10 mL and 20 mL polypropylene unit-dose oral syringe with HDPE plunger (b) (4)

III DATA SUBMITTED TO SUPPORT THE PROPOSED CHANGES

THIS REVIEW ASSESSES ONLY THE RESPONSE FROM THE APPLICANT FOR THE CR COMMENTS CONVEYED TO THE APPLICANT DURING THE PREVIOUS REVIEW CYCLE.

CR Comment #1:

DMF (b) (4) for nimodipine was found to be inadequate to support the submission. The deficiencies must be adequately addressed before this application can be approved. As part of your response, include the date the DMF holder amends the DMF to address the deficiencies.

Response from the applicant:

The DMF holder, (b) (4) submitted an amendment to DMF (b) (4) on 08 October 2019 in response to the FDA DMF Deficiency letter dated 01 August 2019.

☑ Reviewer Evaluation: Adequate

The DMF (b) (4) for manufacturing of drug substance nimodipine was found to be adequate as per the review dated 3/12/2019 by reviewer Dr. Yingzi Wang from Division of Life-Cycle-API. The DMF reviewer found (b) (4) facilities that were used for DS characterization by the DMF holder but were not listed in the NDA application.



Therefore, an information request was sent to the applicant to list these facilities in form 356h and module 3. (b) (4)

(b) (4) Therefore, the applicant did not revised form 356h and module 3. However, as per the guidance *Identification of Manufacturing*

(b) (4)



CR Comment #3:

(b) (4)



CR Comment #4:

Provide stability data for up to at least 6-months to support the proposed packaging configuration and the expiry period.

Response from the applicant:

Stability data through 12 months is included in [Section 3.2.P.8.3](#) in support of a proposed shelf life of 12 months in the proposed pre-filled syringe unit-dose commercial packaging configurations.

Reviewer Evaluation: Adequate

The applicant provided stability data for up to 12 months for three batches of the DP packaged in two new pre-filled syringe configurations. Stability data is also provided for three batches stored at accelerated stability conditions. (b) (4)

(b) (4)

(b) (4)

(b) (4). However, no such trend is noticed for up to 12 months at long-term stability conditions (25°C/60% RH). (b) (4)

(b) (4). However, no concerning trend was noticed for up to 12 months (b) (4)

(b) (4). Stability results are within specification for all testing parameters for all packaging configurations through 12 months under controlled room temperature conditions. This data supports the proposed expiry period of 12-months for new drug product formulation.

CR Comments 5, 6,7:

Include “NDC” before the number displayed on the syringe labels and overwrap labels.

Include description in the dosage form section of the Prescribing Information (PI) to indicate that the oral solution is in fix-dose pre-filled syringe.

List of inactive ingredients in the description section of the PI should be in alphabetical order.

Response from the applicant:

All labeling updates recommended for the syringe labels, overwrap labels, and Prescribing Information (PI) have been included in draft labeling in Section 1.14.1. Please note that the PI for the currently approved formulation is under FDA review for PLLR updates. The PI for the new formulation will be updated to align with the PLLR update, as appropriate, upon approval of this supplement.

☑ Reviewer Evaluation: Adequate

The applicant accepted all labeling recommendations and provided revised carton and container labels and PI. A few more deficiencies (lack of storage conditions and lack warning language regarding refrigeration) were noticed in the container label. These were communicated to the applicant. In response revised labels were provided in an amendment dated 2/26/2020. Based on recommendation from Division of Medication Error Prevention and Analysis (DMEPA), another IR was sent to the applicant to align language regarding storage conditions in the container labels and the PI and to use the term ‘unit-dose’ instead of (b) (4)’. Accordingly, the applicant provided updated labels through an amendment dated 3/20/2020. The labels are also revised to include a few more recommendations as per DMEPA. Below are the revised labels for 30 mg/5mL syringe configuration. Similar labels are provided for 60 mg/10 mL packaging configuration.



Rohit
Kolhatkar

Digitally signed by Rohit Kolhatkar
Date: 3/30/2020 02:27:58PM
GUID: 57bf531500b52a2eccd5395bec77ebc2



David
Lewis

Digitally signed by David Lewis
Date: 3/30/2020 02:28:56PM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of
CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA203340Orig1s011

CLINICAL
PHARMACOLOGY/BIOPHARMACEUTICS
REVIEW(S)

Review and Evaluation of Clinical Data
Review of labelling supplement

NDA	203330 Supplement 11
Supporting Document Number:	e0072, previous submission e0062-0065
Sponsor:	Arbor Pharmaceuticals
Drug:	Nymalize, nimodipine, oral solution
Proposed Indication:	Subarachnoid hemorrhage
Correspondence Date:	12/13/19
Date Received / Agency:	12/13/19
Date Review Completed	3/30/20
Reviewer:	Lawrence Rodichok MD, ODEI, DNP
Materials Reviewed	Resubmission to CR of August 2, 2019

FDA text, *reviewer comment*, extracted from sponsor documents

1. Executive Summary

This is a review of clinical safety data included in an otherwise primarily CMC PAS labelling supplement. The change in labelling is the addition of a new formulation of oral nimodipine. The added formulation is at a higher (2X) concentration of 60 mg in 10 mL whereas the previous formulation was at 60 mg per 20mL. There are also some changes in excipients. The safety data are from a PK study comparing the old and new formulations. The two parts of the study are pooled to allow the maximum number of subjects for review. There were no significant differences between the formulations in the occurrence of clinical adverse events with specific attention to AEs that might be indicative of hypotension, the most common AE with nimodipine. Changes in vital signs are consistent with the hypotension known to occur with nimodipine, but there are no significant differences between the formulations. I recommend approval of the supplement.

1.1. Product introduction

This supplement is a response to a previous Complete Response decision to the original Prior Approval Supplement submitted on April 5, 2019. Subsequent amendments were submitted to address the issues in the CR letter. The supplement is essentially a CMC supplement to support the following reformulation:

(b) (4)
(b) (4)

(b) (4) The reformulation delivers a 60 mg dose of nimodipine in a reduced dosing of 10 mL of oral solution (6 mg/mL), which is an equivalent dose of nimodipine delivered by the current 60 mg/20 mL (3 mg/mL) formulation, (b) (4). In addition, a new unit-dose syringe is also being introduced with the reformulation.

Reviewer Comment: There are clinical safety data from the clinical study comparing the new to the old formulation.

Nimodipine is a dihydropyridine calcium channel blocker approved in 2013 for the treatment of subarachnoid hemorrhage. In humans, nimodipine is rapidly absorbed after oral administration, and peak concentrations are generally attained within 1 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 to 2 hours; a consequence is the need for frequent (every 4 hours) dosing. 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 cytochrome P450 (CYP) 3A4. Because of a high first-pass metabolism, the bioavailability of nimodipine averages 13% after oral administration.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203340s012lbl.pdf

1.2. Conclusions on substantial evidence of effectiveness

Efficacy was not studied.

1.3. Risk-Benefit Assessment

The risk vs. benefit comparison has not changed. This supplement includes clinical data on the safety of a new formulation compared to the previously approved formulation.

2. Therapeutic context

2.1. Analysis of condition

Subarachnoid is a serious and life-threatening condition. A significant proportion of the morbidity and mortality is attributable to delayed cerebral ischemia (DCI) which may be secondary to arterial spasm. Nimodipine is intended to prevent the vasospasm.

2.2. Analysis of current treatment options

There are no other currently approved and marketed drugs for a comparable indication.

3. Regulatory background

3.1. US regulatory action and marketing history

Original approval: 5/10/13

3.2. Summary of Presubmission/Submission Regulatory Activity

See the complete response letter of August 2, 2019

3.3. Foreign Regulatory Actions and Marketing History

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

See the reviews by nonclinical and Clinical Pharmacology

5. Sources of Clinical Data and Review Strategy

This review is limited to the safety data collected during the clinical study comparing the new to the old formulations

6. Review of relevant individual trials used to support efficacy

6.1. Study 1

6.1.1. Study Design

The objectives of this study were:

- To compare the rate of absorption and oral bioavailability of two formulations of Arbor Pharmaceuticals, LLC's Nymalize (nimodipine) Oral Solution, 60 mg/10 mL (Formulation 1; test) and 60 mg/20 mL (Formulation 2; reference), when administered to healthy subjects under fasted conditions
- To evaluate the safety of Nymalize (nimodipine) Oral Solution 60 mg/10 mL (Formulation 1) and Nymalize (nimodipine) Oral Solution 60 mg/20 mL (Formulation 2).

This was an open-label, randomized, two-part study in 30 healthy adult subjects. Part 1 was a pilot, two-period, two-treatment, crossover design in which 6 subjects were enrolled. Part 2 was a pivotal, four-period, two-treatment, full-replicate design in which 24 subjects were enrolled.

This was an open-label study without treatment blinding.

All subjects were dosed after an overnight fast of at least 10 hours. Each study treatment administration was separated by a washout period of at least 3 days.

In study Part 1, subjects received a single dose of each treatment in randomized fashion; one treatment in each study period.

Table 1: Schedule of Assessments

PROCEDURE	Screening	Study Periods 1 to 2 (Part 1) and Study Periods 1 to 4 (Part 2)			End-of-Study/ Early Termination ^a
		Day -1	Day 1	Day 2	
Informed consent	X				
Medical and medication histories	X	X			
ECG	X				X
Vital signs ^b	X		X	X	X
Physical examination	X				X
Oral cavity examination	X				
Serology	X				
Clinical laboratory testing (biochemistry, hematology, urinalysis)	X				X
FSH (postmenopausal female subjects)	X				
Urine drug and cotinine screen	X	X ^c			
Urine alcohol screen		X ^c			
Serum pregnancy test (all female subjects)	X				
Urine pregnancy test (all female subjects)		X ^c			X
Drug administration			X		
Blood sample collection for pharmacokinetic analysis ^c			X	X	
Discharge					X
Adverse events ^d			←	→	→

In study Part 2, subjects received a single dose of each treatment in randomized fashion in Periods 1 and 2. The treatments were repeated using the same sequence during Periods 3 and 4.

Exclusion #2

- Abnormal cardiovascular exam at Screening, including any of the following:
- Prior history of clinically significant abnormal electrocardiogram (ECG), (eg, second- or third-degree heart block, uncontrolled arrhythmia, QTcF [Fridericia’s correction] interval >450 msec for male subjects and >470 msec for female subjects)
- HR <40 bpm or symptomatic bradycardia
- SBP >160 mmHg or <100 mmHg, or symptomatic hypotension
- DBP >95 mmHg
- Prior history of myocardial infarction.

Table 1: Schedule of Assessments

PROCEDURE	Screening	Study Periods 1 to 2 (Part 1) and Study Periods 1 to 4 (Part 2)			End-of-Study/ Early Termination ^a
		Day -1	Day 1	Day 2	
Informed consent	X				
Medical and medication histories	X	X			
ECG	X				X
Vital signs ^b	X		X	X	X
Physical examination	X				X
Oral cavity examination	X				
Serology	X				
Clinical laboratory testing (biochemistry, hematology, urinalysis)	X				X
FSH (postmenopausal female subjects)	X				
Urine drug and cotinine screen	X	X ^c			
Urine alcohol screen		X ^c			
Serum pregnancy test (all female subjects)	X				
Urine pregnancy test (all female subjects)		X ^c			X
Drug administration			X		
Blood sample collection for pharmacokinetic analysis ^c			X	X	
Discharge					X
Adverse events ^d			←	→	

- a) Performed after completion of the 24-hour procedures in Period 2 (study Part 1) or Period 4 (study Part 2) or upon early withdrawal.
- b) Vital signs (blood pressure, pulse rate, and respiration rate) were measured at the following times in each study period: Screening, predose (0 hour) and the following hours postdose: 1, 2, 4, 12, and 24 hours in each study period. Temperature was measured at the following times: Screening, predose (0 hour), and 24 hours postdose in each study period.
- c) Urine drug/alcohol/cotinine screens for all subjects and urine pregnancy tests for female subjects were conducted on Day -1 of Period 1 only.
- d) Blood samples for pharmacokinetic analysis were collected at the following time points in each period: 0 (predose), 10, 15, 30, and 45 minutes and 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours postdose.
- e) Subjects were monitored for any adverse events from the first dose until the end-of-study visit.

6.1.2. Study Results

10.1 Disposition of Subjects

10.1.1 Part 1

A total of 6 subjects participated in Part 1 of study. All 6 of these subjects completed both study periods

10.1.2 Part 2

A total of 24 subjects participated in the study. All 24 of these subjects completed all 4 study periods

Demography

Part 1:

Six subjects were enrolled in Part 1 of the study. There were 3 females and 3 males. Subjects' ages ranged from 27 to 44 years. Subjects' BMI ranged from 24.3 to 30.9 kg/m². Subjects' height and weight ranged from 153.4 to 178.5 cm and 63.6 to

96.4 kg, respectively.

Part 2:

Twenty-four subjects were enrolled in Part 2 of the study. There were 10 females and 14 males. Subjects' ages ranged from 18 to 55 years.

Subjects' BMI ranged from 21.0 to 31.6 kg/m². Subjects' height and weight ranged from 152.8 to 189.3 cm and 54.3 to 104.5 kg, respectively.

Extent of Exposure

Part 1:

All 6 subjects received 1 full dose of Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Formulation 1) and 1 full dose of Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Formulation 2), for a total exposure of 120 mg of nimodipine.

Part 2:

All 24 subjects received 2 full doses of Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Formulation 1) and 2 full doses of Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Formulation 2), for a total exposure of 240 mg of nimodipine.

7. Integrated review of effectiveness – efficacy not assessed

8. Review of Safety

There were no serious adverse events or adverse events that resulted in discontinuation of investigational treatment. Non-serious adverse events are listed in [Table 1](#).

Table 1: AEs by SOC and preferred term, by actual treatment, combined Parts 1 and 2

AEBODSYS	AEDECOD	TRTA = A Nymalize 60mg/10mL N = 30		TRTA = B Nymalize 60mg/20mL N = 30	
		N*	%	N*	%
Gastrointestinal disorders	Constipation	0	0	1	3.3
	Nausea	1	3.3	3	10
General disorders and administration site conditions	Chills	1	3.3	0	0
Musculoskeletal and connective tissue disorders	Back pain	1	3.3	0	0
Nervous system disorders	Dizziness	0	0	2	6.7
	Headache	2	6.7	2	6.7
	Paraesthesia	0	0	1	3.3
Respiratory, thoracic and mediastinal disorders	Oropharyngeal discomfort	0	0	2	6.7
	Oropharyngeal pain	1	3.3	1	3.3
Vascular disorders	Flushing	1	3.3	1	3.3

Source: ADAE By (USUBJID, TRTA, AEBODSYS, AEDECOD) NUSUBJID by TRTA By (AEBODSYS, AEDECOD).jmp

*: N = NUSUBJID

Reviewer Comment: The two studies are combined by treatment group. Treatment A is the new formulation. There is no indication of a difference in the key adverse events of interest, i.e. those related to hypotension such as dizziness or flushing.

Changes in vital signs

The percent change from baseline in systolic blood pressure ([Table 2](#) and [Figure 1](#) below) and diastolic blood pressure ([Table 3](#) and [Figure 2](#)). The change in diastolic blood pressure was somewhat greater than for the systolic blood pressure. In general, the changes were comparable for the two formulations. The reduction in diastolic blood pressure might be more prolonged with the more concentrated formulation.

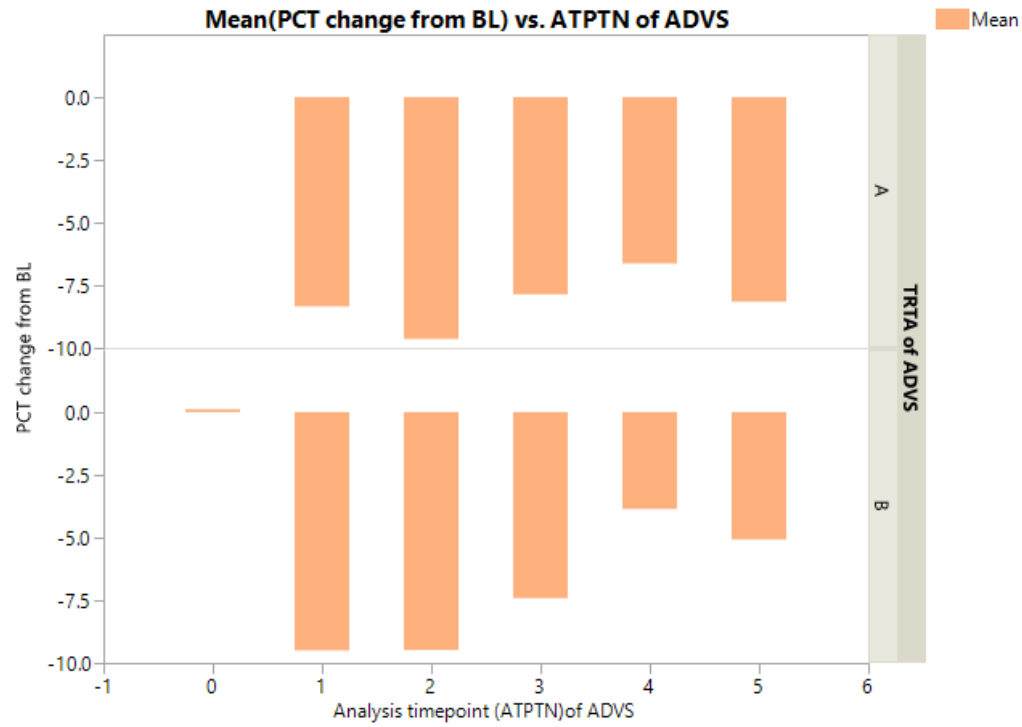
Reviewer Comment: the absence of any associated adverse events suggests that any differences in change in blood pressure between the two formulations is are not clinically relevant.

Table 2: Percent change in Systolic blood pressure before and after dosing, pooled studies

ATPT of ADVS	N	Percent Change from Baseline									
		Mean		Std Dev		Min		Max		Median	
		A	B	A	B	A	B	A	B	A	B
Predose	32	0	0.12	0	2.42	0	-5.7	0	7.79	0	0
1 Hour Postdose	31	-8.3	-9.5	9.33	11.1	-32	-34	5.21	2.86	-6.7	-6.9
2 Hours Postdose	30	-9.6	-9.5	8.78	12	-22	-33	10.4	9.4	-9.9	-12
4 Hours Postdose	30	-7.9	-7.4	7.45	8.95	-18	-23	5.21	10.8	-6.6	-11
12 Hours Postdose	31	-6.6	-3.9	11.5	11.2	-24	-19	19.8	24.8	-7.3	-5.5
24 Hours Postdose	33	-8.2	-5.1	11.8	9.49	-31	-31	11.5	11.2	-5.8	-4.8

Source: VSTEST_SYSBP Subset of Join ADVS c VSBLFL_Y match USUBJID VSTEST AVISIT PCTCHG By (ATPT of ADVS).jmp

Figure 1: Mean percent change from baseline, systolic blood pressure, pooled studies



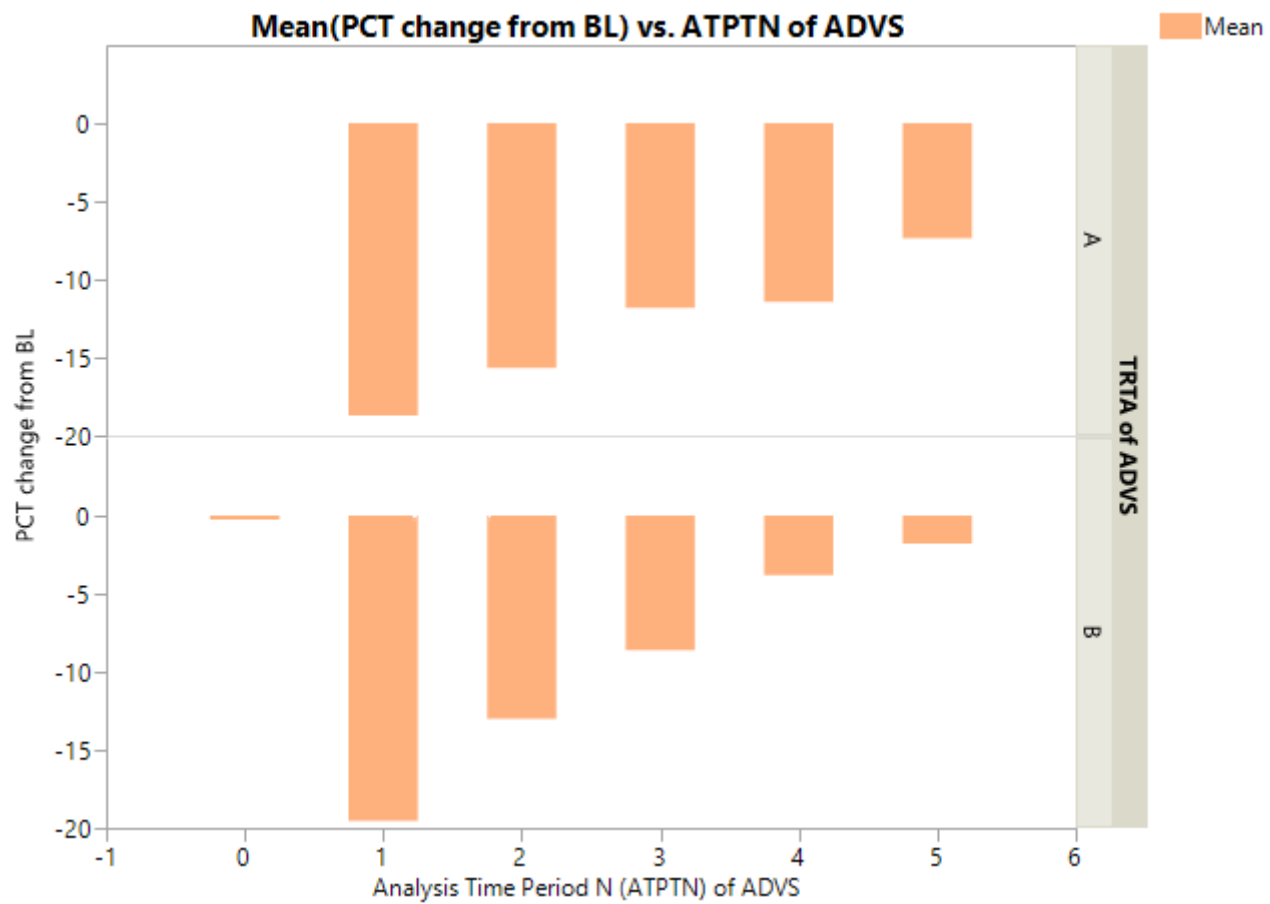
ATPTN	ATPT (Analysis Timepoint)
0	Predose
1	1 Hour Postdose
2	2 Hours Postdose
3	4 Hours Postdose
4	12 Hours Postdose
5	24 Hours Postdose

Table 3: Percent change from baseline, diastolic blood pressure, before and after dosing, pooled studies

VSTPT of ADVS	Percent Change from Baseline										
		Mean		Std Dev		Min		Max		Median	
	TRTA	A	B	A	B	A	B	A	B	A	B
	N										
Predose	32	0	-0.2	0	2.29	0	-8.2	0	4.26	0	0
1 Hour Postdose	31	-19	-20	9.24	9.57	-40	-32	-1.6	-1.7	-15	-20
2 Hours Postdose	30	-16	-13	6.95	11	-30	-30	-8	4.69	-17	-13
4 Hours Postdose	30	-12	-8.6	5.14	10.9	-22	-28	-1.4	11.1	-11	-12
12 Hours Postdose	31	-11	-3.8	9.63	9.72	-30	-24	2.78	16.9	-12	-5.9
24 Hours Postdose	33	-7.4	-1.8	8.78	11	-19	-26	13.3	15.3	-11	1.33

Source: DIABP Subset of Join ADVS c VSBLFL_Y match USUBJID VSTEST AVISIT PCTCHG By (VSTPT of ADVS).jmp

Figure 2: Mean percent change from baseline diastolic blood pressure before and after dosing, pooled studies



The change in pulse rate is shown in **Table 4** and **Figure 3**. Both appear to show an initial increase, followed by a decrease below baseline, followed by an increase that gradually declines but is still above baseline at the final assessment. These changes may be somewhat more prominent with formulation A.

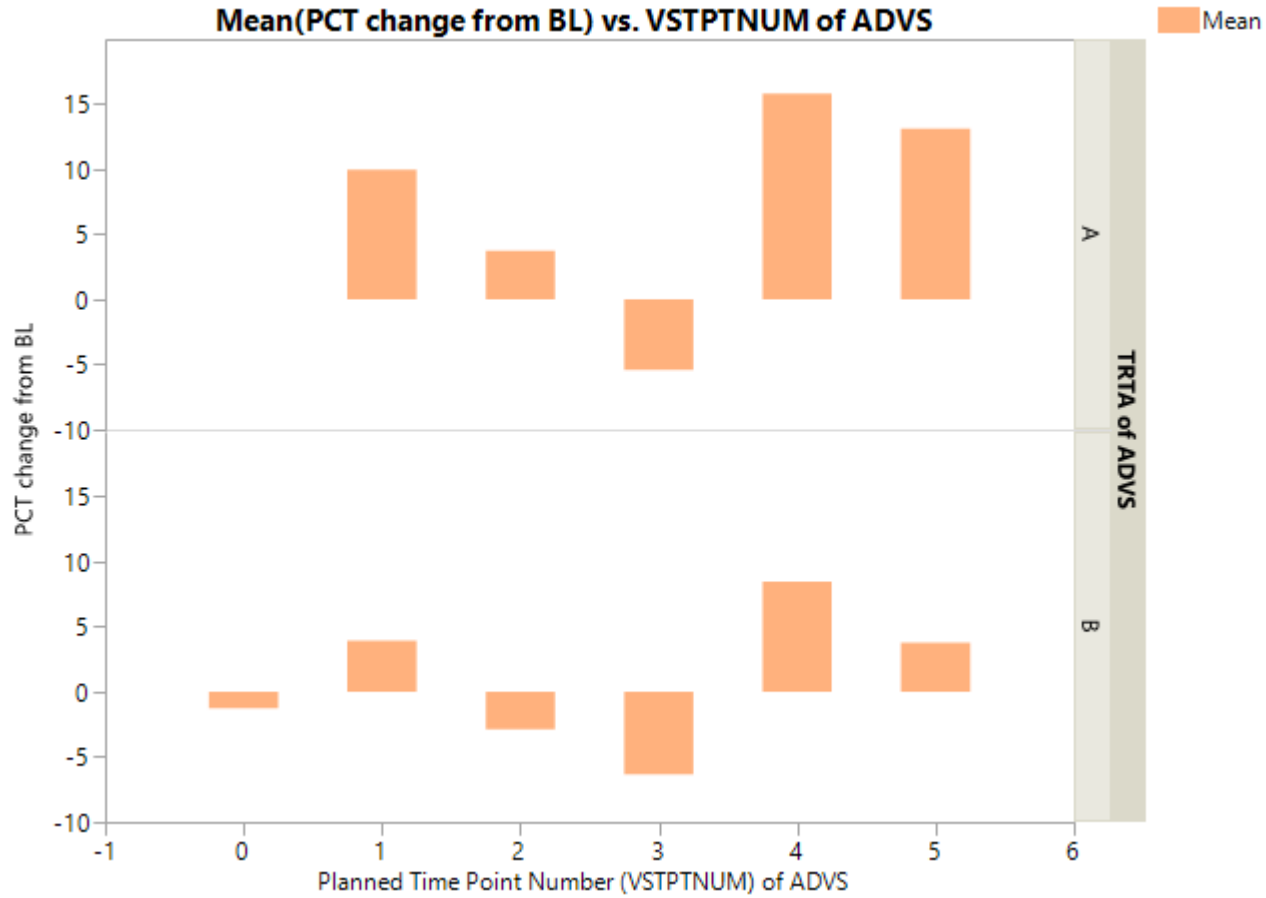
Reviewer Comment: The period of apparent reflex relative bradycardia is of uncertain origin. As for the changes in BP, the changes in pulse rate are comparable by formulation and do not appear to correlate with any clinical adverse events.

Table 4: Percent change in pulse rate, before and after dosing, pooled studies

ATPT of ADVS	STAT	Percent Change from Baseline										
		Mean		Std Dev		Min		Max		Median		
		TRTA	A	B	A	B	A	B	A	B	A	B
		N										
Predose	32	0	-1.2	0	5.11	0	-21	0	0	0	0	
1 Hour Postdose	31	9.97	3.94	10.6	14.2	-6.8	-18	24.6	21.4	11.1	3.51	
2 Hours Postdose	30	3.73	-2.9	6.89	14.6	-11	-26	14.8	23	3.45	-4.8	
4 Hours Postdose	30	-5.4	-6.3	6.98	15.3	-19	-29	4.92	30.4	-4.6	-9.5	
12 Hours Postdose	31	15.8	8.49	12.4	12.9	-1.4	-15	39.7	33.9	14.7	9.22	
24 Hours Postdose	33	13.2	3.8	15.1	13.2	-10	-13	33.3	32.1	8.51	0	

Source: PULSE Subset of Join ADVS c VSBLFL_Y match USUBJID VSTEST AVISIT PCTCHG by TRTA By (ATPT of ADVS).jmp

Figure 3: Mean percent change from baseline, pulse rate, before and after dosing, pooled studies



9. **Advisory Committee Meeting and other external consultations** – Advisory Committee not necessary from a clinical point of view
10. **Labelling recommendations** – see labelling revisions
11. **Risk Evaluation and Mitigation Strategies** – not necessary
12. **Postmarketing Requirements and Commitments** – none recommended

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/s/

LAWRENCE D RODICHOK
03/30/2020 02:23:36 PM

HEATHER D FITTER
04/02/2020 06:04:01 PM

CLINICAL PHARMACOLOGY REVIEW

NDA#	203340/S0072
Submission Date:	12/13/2019
Generic Name:	Nimodipine (Nymalize)
Indication:	Subarachnoid Hemorrhage (SAH)
Sponsor:	Arbor Pharmaceuticals
Reviewer:	Jagan Mohan Parepally, Ph.D.
Submission Type:	Prior Approval Supplement (PAS) to NDA 203340

BACKGROUND

Nymalize (nimodipine oral solution) 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. This is a PAS for the reformulated (non-aqueous) nimodipine oral solution, 60 mg/10 mL. The approved nimodipine oral solution was a lower strength formulation (60 mg/20 mL).

A complete response (CR) letter dated August 02, 2019 was issued in response to a previous PAS. The recommendations in CR letter were related to drug substance and re-formulation of nymalize and to conduct an in vivo bioequivalence (BE) study due to product quality issues. A biowaiver request for the proposed changes in formulation was denied. Refer to CR letter for further details. Following BE study was conducted to support current PAS. At the request of Division of Neurology II, the Office of Scientific Investigations and surveillance (OSIS) declined to conduct audit of the current bioequivalence study, since the study sites were recently inspected. The bioanalytical method validation and analytical performance of assay used to measure plasma concentrations of nimodipine are acceptable.

AR35.001: A Single-Dose, Two-Treatment, Two-Way Crossover (Part 1) and Single Dose, Two Treatment, Full Replicate (Part 2) Bioequivalence Study of Two Different Formulations of Arbor Pharmaceuticals, LLC's Nymalize® (Nimodipine) Oral Solution, in Healthy Adults under Fasted Conditions

Objectives:

- To compare the rate of absorption and oral bioavailability of two formulations of Arbor Pharmaceuticals, LLC's Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Formulation 1; test) and 60 mg/20 mL (Formulation 2; reference), when administered to healthy subjects under fasted conditions
- To evaluate the safety of Nymalize (nimodipine) formulations.

Study Design	This was an open-label, randomized, two-part study in 30 healthy adult
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	<p>subjects.</p> <ul style="list-style-type: none"> Part 1 was a pilot, two-period, two-treatment, crossover design in which 6 subjects were enrolled. Part 2 was a pivotal, four-period, two treatment, full-replicate design in which 24 subjects were enrolled. <p>All subjects were dosed after an overnight fast of at least 10 hours. Each study treatment administration was separated by a washout period of at least 3 days.</p>
Study Population	<p>Healthy male and female subjects aged 18 - 55 years (inclusive), in good health, with a body mass index (BMI) of 18 - 32 kg/m² (inclusive), and a body weight of ≥ 50.0 kg.</p> <p>Number of Subjects: Planned: Part 1: 6; Part 2: 24 Enrolled: Part 1: 6; Part 2: 24 Analyzed: Part 1: 6; Part 2: 24</p>
Treatment Groups	<p>Test Product, Dose: Reformulated (non-aqueous) Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Formulation 1) Dose = 60 mg (10 mL), orally administered</p> <p>Control Product, Dose: Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Formulation 2) Dose = 60 mg (20 mL), orally administered</p> <p>Duration of Treatment: Part 1: Two single-dose treatments were administered with a 3-day washout period between doses in Period 1 and 2</p> <p>Part 2: Two single-dose treatments were administered in Periods 1 and 2. The doses were repeated using the same sequence in Periods 3 and 4. Each dose was separated by a washout period of 3 days between doses.</p> <p>Note: Washout period selected is adequate.</p>
PK Sampling	<p>Blood samples (1 x 6 mL) for the determination of nimodipine were collected at 0 (pre-dose), 10, 15, 30, and 45 minutes and 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 hours post-dose in each study period for Parts 1 and 2.</p>
Pharmacokinetic Assessments	<p>Pharmacokinetic data were analyzed separately for Part 1 and Part 2. The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), last quantifiable concentration (C_{last}), time of the last quantifiable concentration (T_{last}), elimination rate constant (λ_z), terminal half-life (T_{1/2}), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), area under the plasma concentration time curve from time-zero extrapolated to infinity</p>

	(AUCinf), and the percentage of AUCinf based on extrapolation (AUCExtrap). Safety: The Investigator evaluated safety using the following assessments: physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms, and reported or observed adverse events (AEs). Subjects were monitored for any AEs from the first dose through the end of the study.
Safety Assessments	The Investigator evaluated safety using the following assessments: physical examinations, vital sign measurements, clinical laboratory evaluations, electrocardiograms, and reported or observed adverse events (AEs). Subjects were monitored for any AEs from the first dose through the end of the study.
Statistical Methods	<p>Concentration-time data for nimodipine were analyzed using by noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1, Certara, L.P.). Actual sample times relative to dosing were used in the PK analysis. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Actual sample times relative to dosing were used in all pharmacokinetic and statistical analyses.</p> <p>The pharmacokinetic parameters of nimodipine were listed in tables of individual values and aggregated in summary tables by study part and treatment using the following descriptive statistics: n, mean, SD, CV%, minimum, maximum, median, geometric mean, and geometric mean CV%.</p> <p>Part 1 Comparison of the log-transformed pharmacokinetic parameters Cmax, AUClast, and AUCinf for nimodipine across treatments was performed using an analysis of variance (ANOVA) model and the two one-sided t-tests procedure. The ANOVA model included factors for sequence, subject within sequence, treatment, and period. The ratios of the geometric means (test to reference) and 90% confidence intervals were reported. Treatment B was treated as the Reference.</p> <p>Part 2 Comparison of the natural log-transformed pharmacokinetic parameters Cmax, AUClast, and AUCinf, for nimodipine with respect to the test and reference formulations was done using either the two one-sided tests procedure or the reference-scaled procedure depending on the within-subject standard deviation of the reference product (sWR).</p>

	<p>a) If $sWR < 0.294$, the two one-sided tests procedure for a fully replicated design (Proc Mixed) was used to determine bioequivalence for the individual pharmacokinetic parameters. Confidence intervals (90%) were constructed for the treatment ratios (test-to-reference) of C_{max}, AUC_{last}, and AUC_{inf}. The point estimates and confidence limits were exponentiated back to the original scales. Bioequivalence was concluded if the confidence intervals for the three parameters are contained within the limits of 0.8 and 1.25. All evaluable subjects completing at least two study periods, including one test and one reference period, were included in the average bioequivalence (ABE) analysis.</p> <p>b) If $sWR \geq 0.294$, the reference-scaled procedure for a fully replicated design (Proc Mixed) was used to determine bioequivalence for the individual pharmacokinetic parameters. Bioequivalence was concluded if both of the following conditions are satisfied for C_{max}, AUC_{last}, and AUC_{inf}.</p> <ol style="list-style-type: none"> 1. The 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta s^2 WR$ must be ≤ 0, AND 2. The point estimate of the Test/Reference geometric mean ratio must fall within the limits of 0.8 and 1.25. <p>Only subjects completing all four periods were included in the reference-scaled average bioequivalence (RSABE) analysis. Subjects completing both periods for the reference product were used to calculate sWR.</p> <p>A non-parametric method (Wilcoxon signed-rank test) was used to compare the difference in T_{max} between the treatments. Treatment B was treated as the Reference.</p>
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Note: To investigate the comparative bioavailability of two different formulations of nimodipine, a replicate study design was previously used in a literature study¹. Nimodipine is known to exhibit diurnal variation and large with-in subject variability.

Pharmacokinetic Results:

Figure 1: Nimodipine Concentration-Time Data, Mean Plasma Profiles (Part 1) on Linear Scale - Pharmacokinetic Analysis Set

¹ Gualano, V., Ntsikoussalabongui, B., Mignot, A. et al. Comparative Bioavailability of Two Oral Nimodipine Formulations after Administration to 24 Healthy Volunteers. Clin. Drug Investig. 17, 475–482 (1999).

Analyte=Nimodipine

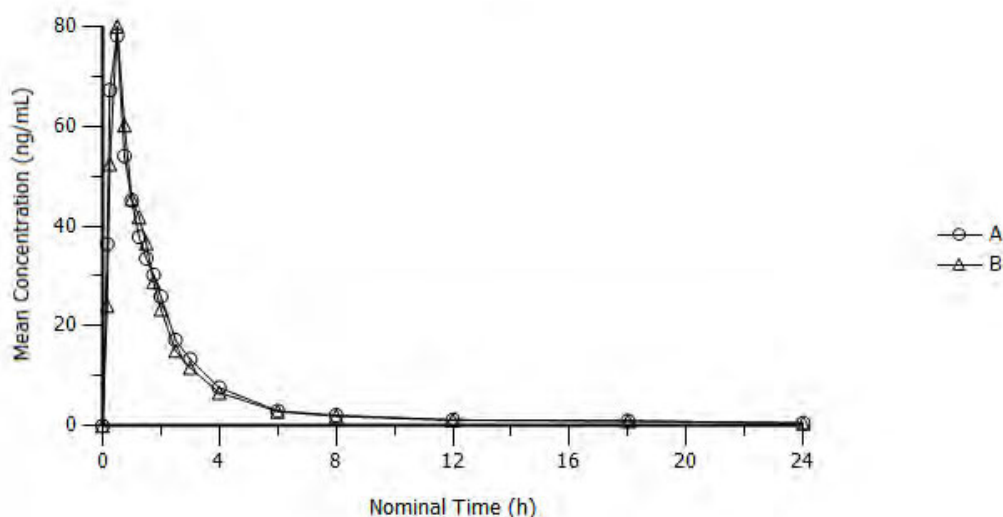


Table 1: Pharmacokinetic Parameters of Nimodipine after Administration of Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Treatment A, Formulation 1) and Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Treatment B, Formulation 2) Part 1

Parameter	Treatment A: Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL				Treatment B: Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (h)	6	0.500 (0.250-0.500)			6	0.500 (0.250-1.50)		
C_{max} (ng/mL)	6	84.1	32.5	38.6	6	84.2	38.8	46.1
AUC_{last} (h*ng/mL)	6	152	37.8	24.9	6	145	38.6	26.7
AUC_{inf} (h*ng/mL)	6	159	38.8	24.4	6	151	41.1	27.1
AUC_{Extrap} (%)	6	4.62	1.96	42.5	6	4.41	1.08	24.5
λ_z (1/h)	6	0.0922	0.0523	56.8	6	0.0799	0.00714	8.94
T_{1/2} (h)	6	8.92	3.20	35.9	6	8.74	0.840	9.61
T_{last} (h)	6	24.0	0.00	0.00	6	24.0	0.0340	0.142
C_{last} (ng/mL)	6	0.562	0.144	25.5	6	0.529	0.192	36.2

Note: T_{max} presented as median (range)

Table 2: Statistical Analysis of Nimodipine after Administration of Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Treatment A, Formulation 1) and Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Treatment B, Formulation 2) Part 1

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
ln(C _{max})	77.8	76.9	101.13	71.92	142.20	0.2634	28.23
ln(AUC _{last})	147	140	105.47	88.76	125.33	0.7214	14.08
ln(AUC _{inf})	155	146	105.72	89.00	125.58	0.7229	14.06

^a Geometric Mean for Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Formulation 1) (Treatment A, Test) and Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Formulation 2) (Treatment B, Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Note: The 90% confidence interval for comparing the maximum and total exposure to nimodipine, based on ln(C_{max}), ln(AUC_{last}), and ln(AUC_{inf}), were not within the 80% to 125% limits. The sample size (n=6) used for part 1 of this study was not adequate based on the variability in PK parameters to draw meaningful conclusions from part1.

Figure 2: Nimodipine Concentration-Time Data, Mean Plasma Profiles (Part 2) on Linear Scale - Pharmacokinetic Analysis Set

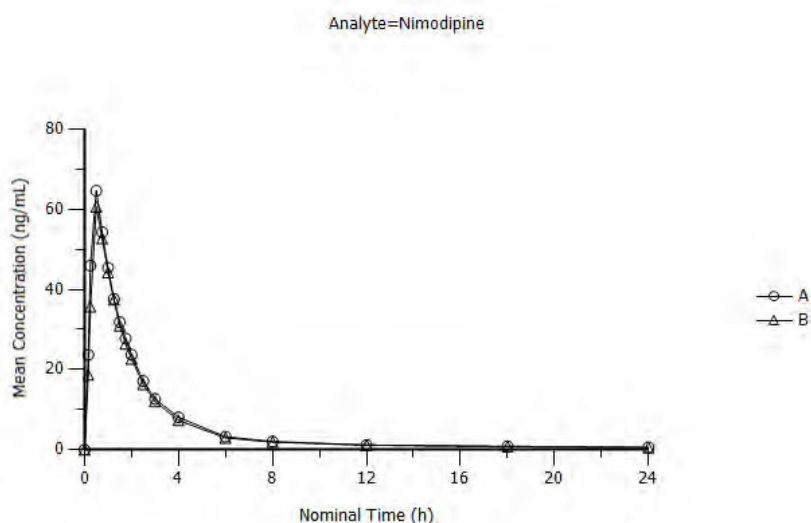


Table 3: Pharmacokinetic Parameters of Nimodipine after Administration of Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Treatment A, Formulation 1) and Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Treatment B, Formulation 2) Part 2

Parameter	Treatment A: Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL				Treatment B: Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (h)	48	0.500 (0.250-1.05)			48	0.500 (0.250-1.82)		
C _{max} (ng/mL)	48	69.9	25.2	36.1	48	67.1	28.1	41.9
AUC _{last} (h*ng/mL)	48	141	50.4	35.8	48	132	45.4	34.3
AUC _{inf} (h*ng/mL)	48	151	54.4	36.0	46	143	50.2	35.0
AUC _{Extrap} (%)	48	6.57	3.60	54.7	46	6.15	2.96	48.2
λ _z (1/h)	48	0.0712	0.0335	47.1	46	0.0677	0.0178	26.4
T _{1/2} (h)	48	11.3	4.28	37.8	46	11.0	3.16	28.7
T _{last} (h)	48	24.0	0.0948	0.395	48	24.0	0.00992	0.0413
C _{last} (ng/mL)	48	0.604	0.306	50.7	48	0.564	0.317	56.2

Note: T_{max} presented as median (range)

The within-subject standard deviation of the reference product (sWR) was < 0.294 for C_{max}, AUC_{last}, and AUC_{inf}; therefore, the two one-sided tests procedure was used to evaluate ln(C_{max}), ln(AUC_{last}), and ln(AUC_{inf}) from Part 2.

Table 4: Statistical Analysis of Nimodipine after Administration of Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Treatment A, Formulation 1) and Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Treatment B, Formulation 2) Part 2

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA	ANOVA
	Test	Ref		Lower	Upper		CV% (Test)	CV% (Ref)
ln(C _{max})	65.8	61.9	106.19	97.86	115.23	0.9965	21.72	23.71
ln(AUC _{last})	132	124	106.43	101.29	111.84	1.0000	11.82	16.83
ln(AUC _{inf})	142	134	106.14	100.29	112.33	1.0000	12.42	17.21

^a Geometric Mean for Nymalize® (nimodipine) Oral Solution, 60 mg/10 mL (Formulation 1) (Treatment A, Test) and Nymalize® (nimodipine) Oral Solution, 60 mg/20 mL (Formulation 2) (Treatment B, Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

The 90% confidence interval for comparing the maximum and total exposure to nimodipine, based on ln(C_{max}), ln(AUC_{last}), and ln(AUC_{inf}), fell within the 80% to 125% limits.

CONCLUSIONS:

The two Nymalize Oral Solution, 60 mg/10 mL (Formulation 1) and 60 mg/20 mL (Formulation 2) are bioequivalent.

Labeling Revisions:

The labeling language described in Section 12.3 was revised to remove promotional language related to absorption of nimodipine.

Jagan Mohan Parepally, Ph.D.
Reviewer
Division of Neuropsychiatric Pharmacology (DNP)

Concurrence:
Angela Men, M.D., Ph.D. _____
Team Leader, DNP

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/s/

JAGAN MOHAN R PAREPALLY
03/26/2020 10:53:52 AM

YUXIN MEN
03/30/2020 08:25:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA203340Orig1s011

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 2, 2020
Requesting Office or Division: Division of Neurology 2 (DN 2)
Application Type and Number: NDA 203340/S-011
Product Name and Strength: Nymalize (nimodipine) oral solution,
30 mg/5 mL and 60 mg/10 mL (proposed)
Applicant/Sponsor Name: Arbor Pharmaceuticals, LLC (Arbor)
OSE RCM #: 2019-810-3
DMEPA Safety Evaluator: Chad Morris, PharmD, MPH
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

On March 31, 2020 Arbor submitted their response to Information Requests sent via email on March 27, 2020 and March 30, 2020 regarding the format of the expiration dates on the carton labeling, overwrap labeling, and container labels. The Division of Neurology 2 (DN 2) requested that we review the response (Appendix A) to determine if it is acceptable from a medication error perspective. The submission is in response to recommendations we made during a previous label and labeling review.^a

2 CONCLUSION

We find the format for the expiration date on the carton labeling, overwrap labeling, and container labels to be acceptable, and we have no additional recommendations at this time.

^a Morris, C. Label and Labeling Review for Nymalize (NDA 203340/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 27. RCM No.: 2019-810-2.

APPENDIX A. IMAGES OF THE IR RESPONSE^b

Question 1:

The format for the expiration date as part of the human-readable product identifier on the carton labeling, required under the Drug Supply Chain Security Act (DSCSA) is not defined. We are unable to assess the expiration date format from a medication safety perspective (for example, may increase the risk for deteriorated drug medication errors). Identify the expiration date format you intend to use as part of the human-readable product identifier on the carton labeling.

USP General Chapter <7> states, "The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All products shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or it shall be sharply embossed, and easily understood (e.g., "EXP 6/13," "Exp. June 13," or "Expires 6/2013")." We are concerned that the proposed expiration date format (that is, YYMMDD using all numerical) will not be easily understood. To minimize confusion and reduce the risk for deteriorated drug medication errors or delays in therapy, revise the format of the expiration date to a format that is "easily understood". The Drug Supply Chain Security Act (DSCSA) guidance on product identifiers recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day in YYYY-MM-DD format if using only numerical characters or in YYYY-MMM-DD if using alphabetical characters to represent the month. FDA recommends using a hyphen or a space to separate the portions of the expiration date.

Arbor Response:

The expiration date format to be used as part of the human-readable product identifier on the carton labeling will be aligned with the recommended YYYY-MM-DD format using all numeric digits.

Question 2:

Additionally, the proposed format for the expiration date (that is, YYYY-MM-DD) on the syringe label and overwrap labeling does not specify whether the month (that is, MM) will be displayed using numerical (for example, 06), or alphabetical (for example, JU) characters. We are unable to assess the expiration date format from a medication safety perspective (for example, may increase the risk for deteriorated drug medication errors). Additionally, clarify whether you intend to use numerical or alphabetical characters to denote the month in your proposed expiration date format.

Arbor Response:

The month in our proposed expiration date format on the syringe and overwrap labeling (YYYY-MM-DD) is intended to be numerical. We would also like to note that the day (DD) included in the expiration date will always be the last day of the month.

^b IR Response available at: <\\cdsesub1\evsprod\nda203340\0078\m1\us\quality-information-amendment.pdf>

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/s/

JOHN C MORRIS
04/02/2020 01:26:18 PM

BRIANA B RIDER
04/02/2020 01:32:26 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 27, 2020
Requesting Office or Division: Division of Neurology 2 (DN 2)
Application Type and Number: NDA 203340/S-011
Product Name and Strength: Nymalize (nimodipine) oral solution,
30 mg/5 mL and 60 mg/10 mL (proposed)
Applicant/Sponsor Name: Arbor Pharmaceuticals, LLC
OSE RCM #: 2019-810-2
DMEPA Safety Evaluator: Chad Morris, PharmD, MPH
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 20, 2020 for Nymalize. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Nymalize (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 FINDINGS AND RECOMMENDATIONS

Table 1. Identified Issues and Recommendations for Arbor Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General			
1.	The format for the expiration date as part of the human-readable	We are unable to assess the expiration date format from a medication safety perspective	Identify the expiration date format you intend to use as part

^a Morris, C. Label and Labeling Review for Nymalize (NDA 203340/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 11. RCM No.: 2019-810-1.

Table 1. Identified Issues and Recommendations for Arbor Pharmaceuticals, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	<p>product identifier on the carton labeling, required under the Drug Supply Chain Security Act (DSCSA) is not defined.</p> <p>Additionally, the proposed format for the expiration date (that is, YYYY-MM-DD) on the syringe label and overwrap labeling does not specify whether the month (that is, MM) will be displayed using numerical (for example, 06), or alphabetical (for example, JU) characters.</p>	<p>(for example, may increase the risk for deteriorated drug medication errors).</p>	<p>of the human-readable product identifier on the carton labeling.</p> <p>Additionally, clarify whether you intend to use numerical or alphabetical characters to denote the month in your proposed expiration date format.</p>

3 CONCLUSION

The revised carton labeling and container labels are unacceptable from a medication error perspective. In Section 2 Table 1, above, we have provided recommendations for Arbor Pharmaceuticals, LLC. We ask the Division convey Table 1 in its entirety to Arbor Pharmaceuticals, LLC so the recommendations are implemented prior to approval of this NDA Supplement.

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/s/

JOHN C MORRIS
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BRIANA B RIDER
03/27/2020 11:13:26 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/11/2020

TO: Division of Neurology
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 203340/S-011

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs 211786, (b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

(b) (4)



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/s/

JAMES J LUMALCURI
03/11/2020 01:11:55 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/11/2020

TO: Division of Neurology
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 203340/S-011

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submission(s): ANDAs 211947, (b) (4).

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observations pertaining to in vivo BE study conduct only:

- (b) (4)

After receiving a written response from the site, OSIS determined that the site's corrective and preventative actions were acceptable. Because, this observation had minimal impact on subject safety and data reliability, and the site's overall study conduct was adequate, OSIS recommended that all study data were reliable to support as regulatory decision. [Final OSIS EIR Review-December 2018 Inspection](#).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials (WCT) Early Phase Services/Bioanalytical Sciences, Inc.	2455 NE Loop 410, Suite 150 San Antonio, TX

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES J LUMALCURI
03/11/2020 01:22:44 PM



NDA 203340/S-011

INFORMATION REQUEST

Arbor Pharmaceuticals, LLC
Attention: Justin Kilby
Senior Manager, Regulatory Affairs
6 Concourse Parkway, Suite 1800
Atlanta, GA 30328

Dear Mr. Kilby:

Please refer to your supplemental New Drug Application (sNDA) dated December 13, 2019, received December 13, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nymalize (nimodipine) oral solution, 60 mg/20 mL.

We are reviewing the Drug Product section of your submission and have the following comments and information requests. We request a prompt written response by February 26, 2020 in order to continue our evaluation of your supplemental NDA.

Comments and information requests:

A. Drug Product

We recommend following changes regarding storage conditions labeling for the 5 mL and 10 mL Syringe labels

- 1) Include 'Rx Only'
- 2) Add storage conditions to the label including the warning 'Do not refrigerate' to align with the warning in the PI.

We recommend following changes regarding storage conditions labeling for the Overwrap bag labels

- 1) Add warning 'Do not refrigerate' to align with the warning in the PI.

We recommend following changes regarding storage conditions labeling for the Carton Labels

- 1) Remove 'Store at room temperature' OR replace it with 'Store at controlled room temperature, USP'
- 2) Add warning 'Do not refrigerate' to align with the warning in the PI.

NDA 203340/S-011

If you have questions, contact Avani Patel, Regulatory Business Process Manager, at (240) 402-1845 or Avani.Patel@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Avani Patel, B.S., Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Avani
Patel

Digitally signed by Avani Patel

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