

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203340Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration**

**Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research**

Date: July 26, 2012

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 203-340 (nimodipine oral solution)

The sponsor (Arbor Pharmaceuticals) has submitted NDA 203-340 for nimodipine oral solution for treatment of subarachnoid hemorrhage. This is a 505(b)(2) application, with Nimotop Capsules (NDA 18-869) specified as the Reference Listed Drug. The related IND for nimodipine oral solution is IND p110870.

Background: Under pIND 110870, the sponsor was informed (*pIND 110870 Preliminary Meeting Comments, 4/26/2011*) that “No additional nonclinical studies will be needed for an NDA unless safety concerns arise (e.g., impurities, degradants) that would require nonclinical safety testing.”

Following the original NDA submission (11/18/2011), several potential review issues were identified, and conveyed to the sponsor in a teleconference on December 7, 2011. From a nonclinical standpoint, the concern was the presence of six specified impurities with acceptance criteria (NMT (b)(4)%) that exceeded the qualification threshold of NMT (b)(4)% (listed in sponsor’s table below). Five of the impurities had not been identified; one (RRT (b)(4)) was stated to be (b)(4).

Test	Acceptance Criteria	Regulatory Analytical Procedure
Assay for Impurities: (b)(4)	NMT (b)(4) NMT NMT NMT NMT NMT NMT NMT	NPLC-1266

The sponsor was informed that additional data would be needed to support the proposed acceptance criteria, e.g., nonclinical studies to qualify or data to demonstrate that the impurity levels in the sponsor's product were similar to those in the approved product. The sponsor provided additional CMC data (January 10, 2012 submission) that demonstrated lower levels (or the absence) of each of the impurities in samples of the marketed capsules (seven lots from three manufacturers); therefore, these data did not support the proposed acceptance criteria. The sponsor responded by lowered the acceptance criteria for all of the listed impurities, except for (b) (4) (RRT (b) (4)). (A change in the wavelength used to detect drug-related peaks, from (b) (4) nm to (b) (4) nm, resulted in slightly different retention times for individual peaks, and a decrease in the number of individual peaks, i.e., impurities originally designated as RRT (b) (4) and (b) (4) were now reported as RRT (b) (4); see sponsor's table below.) Based on the revised acceptance criteria, there are three impurities (RRT (b) (4), (b) (4) and RRT (b) (4)) for which the acceptance criteria are still above the qualification threshold.

Test	Acceptance Criteria	Regulatory Analytical Procedure
Assay for Impurities: (b) (4)	NMT (b) (4) NMT NMT NMT NMT NMT NMT	NPLC-1266

Note: impurity RRT (b) (4) corresponds to RRT (b) (4) and RRT (b) (4) in original table.

The sponsor provided published literature in the original NDA submission to document that (b) (4), thus, qualified at the proposed limit of (b) (4)%. No additional data were provided to qualify the remaining two impurities. However, the sponsor provided an audited draft report of a two-week oral toxicity study in rat to qualify these impurities on May 7, 2012, a revised audited draft report of this study on May 9, 2012, and the final study report (#20025263) on May 18, 2012. The May 9, 2012 submission was considered a major amendment to the NDA, resulting in a three-month extension of the goal date (*Agency letter, dated 5/11/2012*).

Dr. Siarey reviewed the two-week study and, based on his review, concluded that impurities with stability specification limits that exceed the qualification threshold had been adequately qualified and recommended approval of the NDA.

Two-week oral toxicity study: The two-week study was conducted in Sprague-Dawley rat (10/sex/group) and tested "fresh" and "aged/degraded" batches of nimodipine, and purified (b) (4). The aged/degraded batch (L0430) of nimodipine was an expired drug batch which had been stored under accelerated storage condition for 6 months (through November 18, 2011), and then maintained at room temperature protected from light. This batch contained impurities at the following levels: (b) (4)%

Impurity 1, (b)(4)% Impurity 2, (b)(4)% Impurity 3, (b)(4)% Impurity 4, and (b)(4)% (b)(4)
 (b)(4) The purity of the fresh batches (003-005, 003-007) of nimodipine was stated to be (b)(4)%.

Fresh and aged/degraded nimodipine were tested at an initial dose of 60 mg/kg BID (120 mg/kg/day); aged/degraded nimodipine was also tested at a lower initial dose of 30 mg/kg BID (60 mg/kg/day). (The high dose was stated by the sponsor to be a maximum feasible dose.) However, due to clinical signs at 60 mg/kg BID (leading to premature sacrifice in one male) and at 45 mg/kg BID (leading to death or premature sacrifice in females), the high dose was reduced during Days 2-3 to 45 mg/kg BID and then to 45 mg/kg QD; the dose in the low-dose aged/degraded nimodipine group was reduced to 30 mg/kg QD. Therefore, the fresh and high-dose aged/degraded nimodipine groups received 45 mg/kg QD for ≈12 days; low-dose aged/degraded nimodipine group received 30 mg/kg QD for 11-12 days. The group dosed with (b)(4) received a daily dose of (b)(4) mg/kg/day throughout the two-week period.

In animals dying or sacrificed prematurely, severe clinical signs were observed (including unkempt appearance, decreased activity, hypothermia) and terminal studies revealed distension of and abnormal contents in the GI, mild to moderate renal tubule degeneration (correlating with increases in serum creatinine and BUN), necrosis of lymphoid tissue (lymph nodes, thymus, Peyer's patches), and depletion of white pulp in spleen. Although some differences were noted, findings were generally similar in animals receiving fresh and aged/degraded nimodipine. Few clinical signs were evident following nimodipine dose reduction or in animal receiving (b)(4). Findings on other parameters were primarily observed in the animals dying or sacrificed prematurely. In survivors receiving nimodipine (fresh or aged/degraded), drug-related findings included glucose in the urine and increased heart and/or liver weight (with no histopathology correlates); no drug-related (nimodipine or (b)(4)) microscopic findings were detected.

Overall, toxicity findings were similar in animals receiving fresh and aged/degraded nimodipine; few findings were noted following dose reduction to 45 (and 30) mg/kg/day. No findings clearly attributable to (b)(4) were observed.

The percentages of the three impurities in the aged/degraded nimodipine batch, for which the acceptance criteria exceed the qualification threshold, as well as the resulting daily dose at a nimodipine dose of 45 mg/kg /day (or (b)(4) mg/kg/day for (b)(4) alone), are provided in the following table:

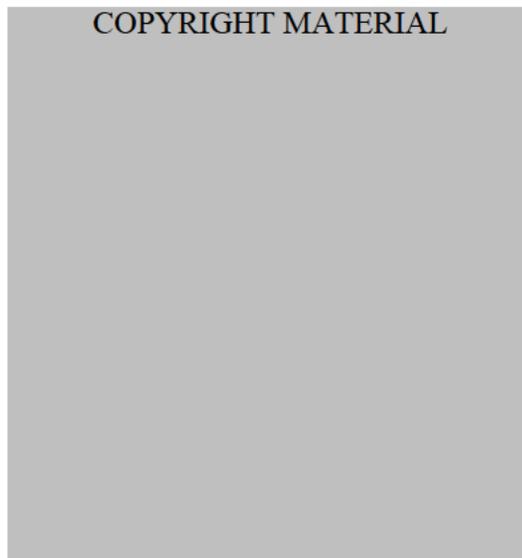
IMPURITY	LEVEL IN AGED/DEGRADED BATCH	RAT DAILY DOSE (mg/m ²)	ACCEPTANCE CRITERIA	MAX HUMAN DAILY DOSE (mg/m ²)
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(b)(4)

The two-week study was of sufficient duration to qualify the impurities, considering the limited duration of the intended clinical use; however, due to toxicity associated with the high dose of nimodipine (fresh and aged/degraded) initially administered, there were only 7/10 HDF that received fresh nimodipine for two weeks and only 5/10 HDF that received aged/degraded nimodipine for that duration. Overall, the two-week study was minimally adequate to qualify these impurities at the doses administered, which provided safety margins of 2-7 compared to the maximum human daily dose.

For [REDACTED] ^{(b) (4)} the sponsor also provided published literature to document that this impurity [REDACTED] ^{(b) (4)}. Only one of the publications provided original human data on nimodipine (Ramsch KD *et al. Am J Nephrol* 6:73-80, 1986). Ramsch *et al.* (1986) reported on the *in vivo* metabolism of nimodipine in six healthy volunteers following a single 60-mg (3 x 20 mg) oral dose of Nimotop. The data on three metabolites (MI = [REDACTED] ^{(b) (4)}) were presented in the following figure (as provided by the sponsor):

Figure 2. Nimodipine Mean Metabolite (MI, MII, MIII) Plasma Concentrations, n=6 healthy subjects. (From Ramsch, et. al., Figure 11.¹)



For comparison, plasma levels of parent compound were 20.6 ± 11.8 ng/mL (C_{\max}) and 42.0 ± 29.4 ng*hr/mL ($AUC_{(0-\infty)}$) with oral tablets (3 x 20 mg). [Plasma levels of nimodipine were higher following oral solution: 116.5 ± 74.3 ng/mL (C_{\max}) and 107.6 ± 51.4 ($AUC_{(0-\infty)}$.)]

These data suggest that [REDACTED] ^{(b) (4)}, with circulating levels (C_{\max}) similar to those of the parent compound; however, the adequacy of these data will be determined by the OCBP review staff.

Recommendations

I concur with Dr. Siarey's recommendation that, from a nonclinical perspective, this NDA is approvable. Regarding labeling, if the approach is to be a straight PLR conversion, based on the latest approved label for Nimotop, only the recommendations for the Highlights section apply. However, the attached table provides recommendations on the nonclinical sections in case labeling is to be revised to reflect current practice and language. These recommendations take into consideration the descriptions provided by Dr. Ed Fisher of the reproductive and developmental toxicity data.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LOIS M FREED
07/26/2012

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 203-340
Supporting document/s: 019
Sequence number: 0013
Applicant's letter date: May 18, 2012
CDER stamp date: May 18, 2012
Product: Nymalize® (Nimodipine)
Indication: Improvement of neurological outcome in patients with subarachnoid hemorrhage (SAH) due to ruptured aneurysms.
Applicant: Arbor Pharmaceuticals
Review Division: Division of Neurology Products
Reviewer: Richard Siarey
Supervisor/Team Leader: Lois Freed
Division Director: Russell Katz
Project Manager: Vandna Kishore

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203-340 are owned by Arbor Pharmaceuticals or are data for which Arbor Pharmaceuticals has obtained a written right of reference. Any data or information described or referenced from a previously approved application that Arbor Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) are for descriptive purposes only and are not relied upon for approval of NDA 203-340.

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

In a 14-day oral study in rats, few and similar toxicity findings were observed in the surviving animals treated with 45 mg/kg/day of fresh and aged nimodipine. Dose levels of the unidentified degradants (impurities 1-4) and (b) (4) (b) (4) at 45 mg/kg/day in the rat are equal or greater than the levels expected at the recommended human dose at the stability specification limits set by the Sponsor; therefore, the degradants are qualified. It is recommended, from the nonclinical perspective, that Nymalize® be approved.

1.1.3 Labeling

A PLR conversion is required for the label; however, there are no nonclinical changes needed. Therefore, there are no labeling issues, from a nonclinical perspective.

1.2 Brief Discussion of Nonclinical Findings

This application is for Nymalize® (nimodipine), an oral version of Nimotop® (capsule). Nimotop® is approved for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V). Nimodipine is an L-type calcium channel blocker.

During the review process, the CMC reviewer identified 5 degradants in drug product batches that needed to be qualified. In order to address this concern, the Sponsor conducted a nonclinical study to assess impurities 1-4 (RRT (b) (4), and (b) (4)) in the aged nimodipine batch (№ L0430) and (b) (4) in the aged nimodipine batch and another test article batch (№ 003-0110) compared to a fresh batch of nimodipine (№'s 003-005 and 003-007). The initial dose chosen for the nimodipine high dose, both fresh and aged, was greater than an MTD, as deaths (4 and 5, respectively) were observed during the first few days of treatment. In animals sacrificed early, toxicity findings occurred in the kidney and lymphoid organ. Although, the deaths occurred after the initial dose, once the dose was reduced to 45 mg/kg/day few toxic findings were observed in the surviving 16 and 15 animals from the fresh and aged groups, respectively. The severity of effects appeared similar between the fresh and aged batches of nimodipine, suggesting that the degradants did not have an additional toxic effect. Although death was observed in the HD groups of both fresh and aged nimodipine treatments, high enough levels of all degradants were administered to cover the levels expected in humans. The toxic findings observed were generally similar between the fresh and aged nimodipine batches.

2 Drug Information

2.1 Drug: Nymalize®

2.1.1 CAS Registry Number: 66085-59-4

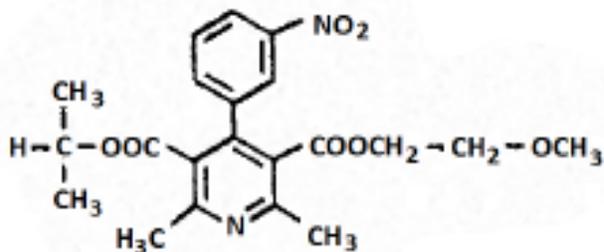
2.1.2 Generic Name: Nimodipine

2.1.3 Code Name: n/s

2.1.4 Chemical Name: Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate

2.1.5 Molecular Formula/Molecular Weight: C₂₁H₂₆N₂O₇; 418.44034 g/mol.

2.1.6 Structure:



2.1.7 Pharmacologic class: L-type Ca channel antagonist.

2.2 Relevant INDs, NDAs, and DMFs

PreIND 110,870 (DNP, treatment to improve the neurologic outcome in patients following subarachnoid hemorrhage from ruptured intracranial berry aneurysms; November 15, 2010).

This is a 505(b)(2) NDA citing NDA 18-869 (approved in 1988, Nimotop® capsules) as the RLD.

For additional information on physical and chemical properties, a Letter of Authorization is provided to (b) (4) Drug Master File (DMF) No (b) (4).

2.3 Clinical Formulation:

2.3.1 Drug Formulation:

The formulation is an oral solution consisting of nimodipine, methylparaben, PEG400, glycerin, sodium phosphate monobasic monohydrate (b) (4) sodium phosphate dibasic dihydrate (b) (4) purified water, and ethyl alcohol (b) (4) %.

Comments on Novel Excipients

None.

Comments on Impurities/Degradants of Concern

The CMC reviewer (May 11, 2012) noted that several degradants in drug product batches needed to be qualified.

2.4 Proposed Clinical Population and Dosing Regimen

The proposed clinical population for Nymalize® is individuals with neurologic dysfunction following subarachnoid hemorrhage from ruptured intracranial berry aneurysms; the dosing regimen is 60 mg in an oral solution every 4 hours.

2.5 Regulatory Background

A meeting request was first submitted to the Agency (DNP) on December 15, 2010, with a meeting package received on February 22, 2011. After responses from the Agency, the pre-IND meeting was cancelled. Subsequently, the Sponsor submitted the NDA on November 18, 2011. The original action date (August 18, 2012) was extended by 3 months due to submission of the 14-day toxicity study report, a major amendment.

3 Studies

3.1 Studies

Other Toxicity Studies

- Impurities
 - A 14-day study of Nimodipine (fresh and degraded) by oral gavage administration in rats.

10 Special Toxicology Studies

10.1 Impurities

Summary for impurities and starting material

Five degradants were detected in the drug product that exceeded the identification and qualification threshold. A study to compare the drug product degradants with the marketed drug (Nimotop® capsules) was unable to qualify all these degradants, as the data from the marketed capsule samples showed lower levels of individual and total degradant when compared to those from the oral solution. In addition, the levels have not been reduced to below the level for qualification (see CMC Review). Therefore, a 14-day toxicology study with fresh nimodipine, aged (LD and HD) nimodipine, and (b) (4) A was conducted. The following tables outline the degradant levels in the drug product.

Table of batch acceptance criteria for stability of to-be-marketed product (Sponsor's)

Test	Acceptance Criteria	Regulatory Analytical Procedure
Appearance/Description Product	(b) (4)	Organoleptique
Appearance/Description Packaging	16 fl. Oz. brown HDPE bottles and white ribbed (b) (4) (b) (4)	Visual
pH	(b) (4)	NPPF-191 / EPS SAS-013
Assay for Nimodipine	(b) (4)% LC	NPLC-1266** / EPS TP-090
Assay for Methylparaben	80.0%-120.0% LC	NPLC-1267** / EPS TP-091
Assay for Impurities: (b) (4)	NMT (b) (4) % NMT (b) (4) % NMT % NMT % NMT % NMT % NMT %	NPLC-1284 / EPS TP-088*
(b) (4)	Reports	Gravimetric
Antimicrobial Effectiveness Testing	Passes test	USP / NPMI-243
Microbial Limits Testing: Total aerobic plate count Total mold & yeast Escherichia coli Salmonella species Staphylococcus aureus Pseudomonas aeruginosa Burkholderia cepacia ^a	NMT (b) (4) cfu/mL NMT (b) (4) fu/mL Negative Negative Negative Negative Negative	USP / NPMI-242 USP / NPMI-242 USP / NPMI-242 USP / NPMI-242 USP / NPMI-242 USP / NPMI-242 USP / NPMI-306

(b) (4)

Tables of batch analysis for the aged product, Batch L0430 (Sponsor's)

(b) (4)

(b) (4)

Certificate of analysis

NCA : (b) (4)
Req :
PO No :
Code Client : (b) (4)
Date spec :
Version : 1

Printed : 2011-12-28
Received : 2011-11-18
Closed : 2011-12-28

Arbor Pharmaceuticals Inc./Allison Lowry
980 Hammond Drive, Suite 1250
Atlanta, Georgia 30328

Page : 1 of 2

Sample : NIMODIPINE ORAL SOLUTION, 60 MG/20 ML

Section : 1

Lot No : L0430 *

Template : Stability, Specification: NIM001.04, Protocol: P091-PSTB1-005

Description : Clear yellow liquid solution.

Conforms

TEST	METHOD	SPECIFICATION	RESULT
Appearance/Description Packaging	Visual	16 fl. Oz	(b) (4)
Assay of Nimodipine	NPLC-1266		(b) (4)
pH	USP <791>		(b) (4)
Assay of Methylparaben	NPLC-1267		(b) (4)
Impurities: Any unspecified individual impurity	NPLC-1266		(b) (4)
	(b) (4)		(b) (4)
	NPLC-1266		(b) (4)

Lot notes:

Verified by :

(b) (4)

Approved by :
Chemist

(b) (4)

unless in full, is permitted without written authorization.

TEST	METHOD	SPECIFICATION	RESULT
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Lot: L0430

(A) 16 fl. Oz HDPE bottle cannot be determined visually.

(B) Result based on the density value supplied by hte customer ((b) (4) mL).

(C) RRT (b) (4) RRT (b) (4)%, (b) (4)

(D) RRT (b) (4)%, RRT (b) (4)%

(E) RRT (b) (4)%, RRT (b) (4)%

		6 Months			
Name or RRT if Unspecified	% a/a Impurity	Name or RRT if Unspecified	% a/a Impurity	Name or RRT if Unspecified	% a/a Impurity
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Study title: A 14-day study of Nimodipine (fresh and degraded) by oral gavage administration in rats

Study no.: 20025263

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: February 23, 2012

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Nimodipine Oral Solution (expiry date Nov 18, 2011, 6 month accelerated storage), Batch № L0430, (b) (4) with (b) (4) of (b) (4), (b) (4) of (b) (4) and (b) (4) (b) (4) (b) (4) (b) (4) Batch № 003-011, 100%

Control: Placebo (Methylparaben), Batch № 003-004, 100%

Fresh Nimodipine Oral Solution, Batch №'s 003-005, 003-007, (b) (4) and (b) (4)

Key Study Findings

- Mortality occurred at doses greater or equal to 90 mg/kg/day.
- Group 2 and 4 animals that died or were sacrificed early had histopathological findings that included mild to moderate degeneration of the tubules in the

kidneys, mild to moderate lymphoid depletion of the white pulp in the spleen, and minimal to moderate lymphoid necrosis in the lymph nodes, thymus, and Peyer's patch.

Methods

Doses: See table below
 Frequency of dosing: Twice daily (b.i.d.; see table below)
 Route of administration: Oral (gavage)
 Dose volume: 10-20 ml/kg (see table below)
 Formulation/Vehicle: Placebo (methylparaben)
 Species/Strain: Rat/Sprague-Dawley
 Number/Sex/Group 10
 Age: Approximately 8 weeks at start of treatment
 Weight 241-357 g (males), 187-241 g (females)
 Deviation from study protocol: See study design table below

Study design (Sponsor table)

Group No.	No. of Main Animals		Test Material	Dose Level (mg/kg/dose)	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg/dose)
	Males	Females					
1	10	10	Placebo	0	0 ^a	0	20/15 ^b
2	10	10	Nimodipine (fresh)	60/45 ^b	120/90/45 ^{a,b}	3	20/15 ^b
3	10	10	Nimodipine (aged/degraded)	30	60/30 ^a	3	10
4	10	10	Nimodipine (aged/degraded)	60/45 ^b	120/90/45 ^{a,b}	3	20/15 ^b
5	10	10	(b) (4)				

- ^a Beginning on Day 3 for the males and Day 2 for the females, the frequency of dosing was reduced from twice daily to once per day for Groups 1-4, resulting in reductions of the dose levels to 45 mg/kg/day for Groups 2 and 4 and to 30 mg/kg/day for Group 3.
- ^b Beginning on Day 2 for the males and Day 1 for the females, the dose volume was reduced to 15 mL/kg/dose in Groups 1, 2, and 4. This resulted in a reduction of the dose levels to 45 mg/kg/dose or 90 mg/kg/day for Groups 2 and 4.
- ^c Beginning on Day 1, the animals in Group 5 were dosed once per day.

Observations and Results

Margins for degradants to the Sponsor's proposed stability specifications

	Stability	Human dose	Impurity level	Rat dose of	
	acceptance	of Impurity*	in aged batch	impurity	Margin
Impurity	criteria	(ma/ka) (ma/m ²)	№ L0430	(ma/ka) (ma/m ²)	(ma/m ²)

(b) (4)					
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* At 6 mg/kg/day nimodipine (assumes 60 kg human).
^aNimodipine Batch № L0430 (45 mg/kg/day); (b) (4) (b) (4) Batch № 003-011 ((b) (4)

Mortality

Observations were made twice daily, in the morning and afternoon.

Mortality was observed on Day 2 in 1 M and 3 F from Group 2 and in 5 F from Group 4 (see table below). On Day 2 for M and Day 1 for F, the dose for Groups 2 and 4 was reduced from 60 mg/kg b.i.d. (120 mg/kg/day) to 45 mg/kg b.i.d. (90 mg/kg/day); this was accomplished by reducing the dose volume from 20 ml/kg to 15 ml/kg. The dose volume for Group 1 was also reduced from 20 ml/kg to 15 ml/kg to correspond to the volume given to Groups 2 and 4; 20 ml/kg was the highest dosing volume used in the study (see study design table above). Due to continued adverse clinical signs in M (on Day 3) and adverse clinical signs and mortality in F (on Day 2), the dose was again reduced, on Day 3 for M and Day 2 for F, from b.i.d. to q.d. for Groups 1-4. No further mortalities were observed.

Macroscopic findings in animals that died early included distention of the cecum and stomach; pale carcass; and abnormal contents in the GI tract (duodenum, ileum, jejunum, cecum, colon, and rectum). Microscopic findings in F included mild to moderate degeneration of the tubules in the kidneys that correlated with individual increases in serum urea nitrogen and creatinine observed at time of sacrifice of the moribund animals. The Sponsor considered the kidney findings the likely cause of death or moribund condition.

Table of animal mortality (Sponsor's)

Group	Animal No./Sex	Found Dead or Euthanized Moribund	Dose(s) Received
2	2438/M	Euthanized Moribund	60 mg/kg/dose (2 doses) and 45 mg/kg/dose (1 dose)
2	2490/F	Euthanized Moribund	45 mg/kg/dose (2 doses)
2	2492/F	Euthanized Moribund	45 mg/kg/dose (2 doses)
2	2494/F	Euthanized Moribund	45 mg/kg/dose (2 doses)
4	2507/F	Euthanized Moribund	45 mg/kg/dose (2 doses)
4	2508/F	Found Dead	45 mg/kg/dose (2 doses)
4	2509/F	Euthanized Moribund	45 mg/kg/dose (2 doses)
4	2511/F	Euthanized Moribund	45 mg/kg/dose (2 doses)
4	2513/F	Euthanized Moribund	45 mg/kg/dose (3 doses)

Clinical Signs

Observations were performed daily during treatment, 3 hours post-dose. Each animal had a detailed examination weekly, from Week -1.

Clinical findings of fecal stain, soft stools, diarrhea and urine stain were observed generally in Groups 1-4 on Days 2-3. These findings occurred in all groups and were generally similar between Group 2 and 4 animals. Occurrences of these findings were only sporadic, from Days 4-15 in M and Days 3-15 in F, after the reduction of dose to 45 mg/kg/day in Groups 2 and 4.

Findings included distended abdomen and red pinna(e)/extremities observed in Groups 2 and 4 M, and decreased activity, hypothermia, slow breathing, partially closed eyelids, and wobbly gait observed in Groups 2 and 4 F; these findings were generally not

observed in Group 1 animals. The findings were generally observed on Day 2 and primarily in animals that were euthanized moribund.

Clinical signs in M or F administered (b) (4) were observed primarily on Days 14 or 15, and consisted of soft stools, fecal stain, and red pinna(e)/extremities.

Body Weights

Body weights were recorded once pre-treatment and on Days 1, 8, and 14.

In M, nimodipine decreased mean body weight gain. At Day 14, body weight gain, compared to group 1 (placebo), was -11% in Group 2, -15% in Group 4, and -18% in Group 5 M. In F, body weight gain was only decreased (27%) in Group 5. It should be noted that treatment of Group 5 was started a week later than in Groups 1-4; therefore, absolute weights cannot be directly compared.

Table of body weight gains

Group	Dose (mg/kg/day)	Day 1-8		Day 8-14		Day 1-14							
		Male	Female	Male	Female	Male	Female						
Control		45 g	0%	19 g	0%	43 g	0%	18 g	0%	88 g	37 g		
Fresh Nim.	120 [#] /90/45	38 g	-16%	20 g	+5%	40 g	-7%	18 g	0%	78 g	-11%	38 g	+3%
Aged Nim.	60/30	55 g	+22%	25 g	+32%	48 g	+12%	14 g	-22%	103 g	+17%	39 g	+5%
Aged Nim.	90/45	33 g*	-27%	22 g	+16%	42 g	-2%	23 g	+28%	75 g	-15%	45 g	+22%
	(b) (4)	43 g	-4%	14 g	-26%	29 g*	-33%	13 g	-28%	72 g	-18%	27 g	-27%

Nim. – nimodipine. (b) (4) statistically significant.

Food Consumption

Food consumption was recorded weekly during from Week -1 and during treatment.

There were no changes in food consumption over the course of treatment (see table below).

Table of food consumption

Group	Dose (mg/kg/day)	Day 1-8		Day 8-14		Day 1-14							
		Male	Female	Male	Female	Male	Female						
Control		27 g	0%	18 g	0%	32 g	0%	22 g	0%	59 g	40 g		
Fresh Nim.	120 [#] /90/45	24 g	-11%	20 g	+11%	31 g	-3%	23 g	+5%	55 g	-7%	43 g	+8%
Aged Nim.	60/30	30 g	+11%	20 g	+11%	32 g	0%	22 g	0%	62 g	+5%	42 g	+5%
Aged Nim.	90/45	24 g	-11%	19 g	+6%	31 g	-3%	24 g	+9%	55 g	-7%	43 g	+8%
	(b) (4)	30 g	+11%	20 g	+11%	30 g	0%	21 g	-5%	60 g	+2%	41 g	+3%

Nim. – nimodipine. (b) (4)

Ophthalmoscopy

Examinations were performed pre-treatment (Day -4 for Groups 1-4 F, Day -5 for Groups 1-4 M, and Day -11 for Group 5 animals) and during the last week of treatment (Day 11 for Groups 1-4 F, and Day 12 for Groups 1-4 M and group 5 animals).

Moderate hemorrhage was observed in the vitreous of 1 Group 2 M and the iris of 1 Group 5 F, retinal detachment and moderate persistent hyaloids remnant were observed in 1 Group 5 F, and 1 Group 2 M had slight cataract. Corneal crystals (slight) developed in both eyes of 1 Group 1 M, 3 and 1 Group 2 M and F, 4 and 2 Group 3 M and F, 2 and 1 Group 4 M and F, and 2 and 1 Group 5 M and F.

Hematology

Blood samples were taken in on Day 15, or before an unscheduled euthanasia. The following parameters, as listed in the study report, were assessed.

Red blood cell count	White blood cell count
Hemoglobin concentration	Neutrophil count
Hematocrit	Lymphocyte count
Mean corpuscular volume	Monocyte count
Mean corpuscular hemoglobin concentration	Eosinophil count
Mean corpuscular hemoglobin	Basophil count
Reticulocyte count (absolute)	Large unstained cells
Platelet count	Other cells (as appropriate)
Red cell distribution width	
Activated partial thromboplastin time	Prothrombin time

The major changes in hematology parameters were observed in animals from Groups 2 and 4 that were sacrificed moribund on Day 2. These changes included increases in RBC count, HGB, HCT, monocytes, and neutrophils, and decreases in WBC count, lymphocytes, and eosinophils. In Groups 3-5 animals that survived to Day 15, statistically significant changes were observed in some hematological parameters, but these were generally small or similar to Group 2 animals. Statistical significant increases in APTT and PT were observed in Group 5 M (15%) and F (5%), respectively.

Table of RBC parameter changes

Group (mg/kg/day)	Dose	RBC Count				HGB				HCT			
		Male		Female		Male		Female		Male		Female	
		D2 [#]	D15										
2	120/90/45	+24%	+5%	+17%	+2%	+21%	+4%	+16%	+6%*	+35%	+6%*	+35%	+6%*
3	60/30		+4%		+4%		+2%		+5%*		+4%		+7%*
4	90/45		+4%		+10%		+8%*		+2%		+16%		+7%*
5	7.5		+6%*		+2%		+3%		0%		+3%		+1%

comparison with Day 15 placebo (group 1) values. *statistically significant.

Table of WBC parameter changes

Group (mg/kg/day)	Dose	WBC Count				Lymphocytes				Monocytes			
		Male		Female		Male		Female		Male		Female	
		D2 [#]	D15										
2	120/90/45	-11%	+8%	-28%	-13%	-80%	0%	-62%	-15%	+54%	+20%	+60%	7%
3	60/30		-4%		-7%		-5%		-4%		+5%		-12%
4	90/45		-13%		-55%		+14%		-15%		-79%		+8%
5	(b) (4)		-10%		-13%		-9%		-13%		-41%		-31%

comparison with Day 15 placebo (group 1) values.

Table of WBC parameter changes (continued)

Group (mg/kg/day)	Dose	<u>Neutrophils</u>				<u>Eosinophils</u>				<u>LUC</u>			
		Male		Female		Male		Female		Male		Female	
		D2 [#]	D15	D2 [#]	D15	D2 [#]	D15	D2 [#]	D15	D2 [#]	D15	D2 [#]	D15
2	120/90/45	+250%	+39%	+137%	-8%	-83%	+48%	-82%	-22%	+49%	-14%	-29%	+12%
3	60/30		+1%		-22%		+10%		-26%		-25%		+5%
4	90/45		-5%	+75%	+35%		-7%	-91%	+18%		-37%	-76%	+19%
5	(b) (4)		-10%		-5%		+42%		-27%		-70%		-55%

comparison with Day 15 placebo (group 1) values.

Clinical Chemistry

Blood samples were taken in on Day 15, or before an unscheduled euthanasia. The following parameters, as listed in the study report, were assessed.

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin
Gamma-glutamyltransferase	Albumin/globulin ratio
Total bilirubin	Glucose
Urea nitrogen	Cholesterol
Creatinine	Triglycerides
Calcium	Sodium
Phosphorus	Potassium
	Chloride

The major changes in biochemical parameters were observed in animals from Groups 2 and 4 that were sacrificed moribund on Day 2 (see tables below). These changes included increases in AST, AP, ALT, GGT, bilirubin, cholesterol, triglycerides, total protein, albumin, globulin, glucose, urea nitrogen, creatinine, calcium, phosphorus, sodium, potassium, and chloride. In Groups 3 and 4 animals that survived to Day 15, statistically significant changes were observed in some biochemical parameters, but these were generally small or similar to Group 2 animals. However, there were statistically significant changes in Group 5 animals that included increases in globulin, glucose, urea nitrogen, and creatinine, and decreases in triglycerides, albumin, A/G ratio and calcium.

Tables of biochemical changes in moribund Group 2 and 4 animals on Day 2 (comparisons made with Day 15 Group 1)

Group (mg/kg/d)	Dose	<u>AST</u>		<u>AP</u>		<u>ALT</u>		<u>GGT</u>		<u>Bilirubin</u>		<u>Cholesterol</u>	
		Male	Female	Male	Female	Female	Female	Male	Female	Male	Female		
2	120/90/45	+97%	+188%	+238%	+488%	+386%	+25500%	+77%	+169%	+194%	-27%		
4	90/45		+96%		+334%	+205%	+16125%		+38%		+11%		

Group (mg/kg/d)	Dose	<u>TriG</u>		<u>Protein</u>		<u>Albumin</u>		<u>Globulin</u>		<u>Glucose</u>	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2	120/90/45	+66%	+59%	+56%	+23%	+32%	+16%	+91%	+34%	+216%	+733%
4	90/45		+350%		+25%		+15%		+41%		+915%

Group	Dose (mg/kg/d)	Urea Nitrogen		Creatinine		Calcium		Phosphorus		Sodium	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2	120/90/45	+767%	+565%	+581%	+711%	+19%	+12%	+190%	+259%	+24%	+7%
4	90/45		+576%		+607%		+17%		+238%		+10%

Group	Dose (mg/kg/d)	Potassium		Chloride	
		Male	Female	Male	Female
2	120/90/45	+30%	+32%	+25%	-1%
4	90/45		7%		5%

Tables of biochemical changes in on Day 15

Group	Dose (mg/kg/d)	TriG		Bilirubin		Albumin		Globulin		A/G Ratio	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2	120/90/45	-2%	+13%	-24%*	-12%	-1%	+1%	+3%	+4%	-3%	-4%
3	60/30	+7%	-3%	-18%	-12%	+1%	+3%	+5%	+6%	-5%	-4%
4	90/45	-14%	+10%	-19%*	-10%	+2%	+3%	+1%	+8%	+1%	-6%
5	(b) (4)	+9%	-26%*	-1%	-12%	-5%*	-8%*	+14%*	+6%	-17%*	-14%*

Group	Dose (mg/kg/d)	Glucose		Urea Nitrogen		Creatinine		Calcium		Phosphorus	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
2	120/90/45	-9%	+15%	+32%	+15%	+1%	+6%	-1%	-4%	-5%	-16%*
3	60/30	+3%	+13%	+15%	+4%	+1%	0%	-1%	-3%	-3%	-14%*
4	90/45	-1%	+18%	+37%*	-6%	+6%	+3%	-2%	-3%	-7%	-16%*
5	(b) (4)	+31%*	+31%*	+67%*	+5%	+32%*	-3%	-6%*	-5%*	-10%	+4%

*statistically significant.

Urinalysis

Urine samples were taken overnight on Day 15. The following parameters, as listed in the study report, were assessed.

Color	Protein
Clarity	Glucose
Specific gravity	Bilirubin
Microscopic evaluation of urine sediment	Ketones
Total Volume	Blood
pH	

Compared to control animals, there was a statistical increase in urinary pH in Groups 2-4 M, with fresh and aged increased by a similar amount. In F, there was an increase in glucose, the increase was greater in Group 4 F.

Gross Pathology

Gross pathology was assessed in all animals.

The macroscopic findings were generally unremarkable. The main finding in animals that survived treatment (scheduled euthanasia on Day 15) was abnormal contents in the GI tract (cecum, colon, and rectum); this was observed in animals of all groups.

Table of macroscopic GI tract findings in animals that survived treatment (Sponsor's)

Group	No. animals examined	Males/Females				
		1 10/10	2 9/7	3 10/10	4 10/5	5 10/10
Cecum						
	Abnormal contents	6/8	6/6	6/8	7/4	3/5
Colon						
	Abnormal contents	1/4	4/4	0/3	4/2	3/5
Rectum						
	Abnormal contents	4/2	2/2	2/2	6/2	1/3

The most frequent macroscopic findings in animals that died early included distention of the cecum and stomach, pale carcass, and abnormal contents in the GI tract.

Organ Weights

At necropsy, the organs listed in the table below from the study report, were weighed.

Brain	Kidney ^a
Epididymis ^a	Liver
Gland, adrenal ^a	Lung
Gland, pituitary	Ovary ^a
Gland, prostate	Spleen
Gland, seminal vesicle	Testis ^a
Gland, thyroid (including parathyroid) ^a	Thymus
Heart	Uterus

^a Paired organ weight.

A statistically significant increase was observed in relative mean heart weight in M (11% and 17%) and F (17% and 20%) and in relative mean liver weight in F (14% and 30%) of Group 2 and 4 animals, respectively. A statistically significant increase in M (10%) and F (10%) relative mean lung weight was only observed in Group 4 animals.

In Group 5 M, a decrease in relative mean spleen (15%) and thymus weights (18%) and a statistically significant decrease in relative mean brain (11%) and kidney (7%) weights were observed. No statistically significant changes were observed in Group 5 F.

Table of organ changes in absolute weight compared to control animals (adapted from Sponsor's table)

	Brain	Heart	Kidney	Liver	Spleen	Seminal Vesicle	Epididym /Uterus	Testes/ Ovary	Lung	Thymus	Thyroid	Adrenal	Pit G
Male													
Fresh:	0%	+7%	-7%	-2%	-5%	-9%	+1%	+1%	+2%	-8%	-13%	-2%	+6%
Aged LD:	-1%	+12%*	-4%	+5%	-2%	-15%	+4%	+4%	+5%	+4%	+2%	+3%	-1%
Aged HD:	-1%	+12%*	-5%	-2%	-14%	-6%	0%	-3%	+5%	-15%	+3%	-2%	-1%
A:	2%	+9%	+6%	+15%*	-3%	+10%	+17%*	+2%	+14%*	-6%	+5%	+7%	+9%
Female													
Fresh:	-1%	+15%*	-6%	+12%	-3%	-	+3%	-4%	+4%	+1%	+14%	+4%	-7%
Aged LD:	+3%	+18%*	-4%	+9%	+5%	-	+13%	+14%	+7%	+14%	+5%	+2%	0%
Aged HD:	+2%	+24%*	-4%	+35%*	+19%	-	+9%	+24%*	+14%*	+28%	+12%	+6%	-3%
A:	+2%	-2%	-1%	-3%	-5%	-	+31%	-6%	+2%	-11%	+17%	+7%	-6%

A – (b) (4) Epididym – epididymis, Pit G – Pituitary, *statistically significant.

Table of organ changes in weight (relative to body weight) compared to control animals (adapted from Sponsor’s table)

	Brain	Heart	Kidney	Liver	Spleen	Seminal Vesicle	Epididym /Uterus	Testes/ Ovary	Lung	Thymus	Thyroid	Adrenal	Pit G
Male													
Fresh:	+4%	+11%*	-3%	+3%	-1%	-5%	+5%	+5%	+6%	-4%	-9%	+2%	+11%
Aged LD:	-5%	+8%	-8%*	0%	-7%	-19%	0%	0%	0%	-1%	-3%	-1%	-6%
Aged HD:	+4%	+17%*	-1%	+3%	-10%	-2%	+4%	+2%	+10%*	-11%	+8%	+3%	+4%
A:	-11%*	+5%	-7%*	0%	-15%	-5%	+1%	-11%	0%	-18%	-9%	-7%	-5%
Female													
Fresh:	+1%	+17%*	-4%	+14%*	-1%		+4%	-3%	+7%	+2%	+16%	+6%	-5%
Aged LD:	0%	+15%*	-6%	+7%	+3%	-	+11%	+11%	+5%	+12%	+3%	0%	-2%
Aged HD:	-1%	+20%*	-7%	+30%*	+15%	-	+5%	+19%	+10%*	+24%	+9%	+3%	-7%
A:	-1%	-4%	-4%	-5%	-8%	-	+28%	-9%	-1%	+13%	+14%	+4%	-9%

A – (b) (4) (b) (4) Epididym – epididymis, Pit G – Pituitary, *statistically significant.

Histopathology

At necropsy, the following organs, listed in the study report, were prepared for histopathology examination. Tissues were fixed in 10% formalin, except for testes (fixed in Modified Davidson’s solution) and optic nerve (fixed in Davidson’s solution), and stained with hematoxylin and eosin.

Animal identification	Large intestine, colon
Artery, aorta	Large intestine, rectum
Bone marrow smear ^a	Liver
Bone marrow, femur	Lung
Bone marrow, sternum	Lymph node, mandibular
Bone, femur	Lymph node, mesenteric
Bone, sternum	Muscle, skeletal
Brain	Nerve, optic ^b
Cervix	Nerve, sciatic
Epididymis	Ovary
Esophagus	Oviduct
Eye ^b	Pancreas
Gland, adrenal	Skin
Gland, harderian	Small intestine, duodenum
Gland, lacrimal	Small intestine, ileum
Gland, mammary	Small intestine, jejunum
Gland, parathyroid	Spinal cord
Gland, pituitary	Spleen
Gland, prostate	Stomach
Gland, salivary	Testis ^c
Gland, seminal vesicle	Thymus
Gland, thyroid	Tongue
Gross lesions/masses	Trachea
Gut-associated lymphoid tissue	Ureter
Heart	Urinary bladder
Kidney	Uterus
Large intestine, cecum	Vagina

^a Bone marrow smears were allowed to air dry and were not fixed in formalin.

^b Preserved in Davidson’s fixative.

^c Preserved in Modified Davidson’s fixative.

Adequate Battery: Yes.

Peer Review: No.

Signed Pathology report: Yes, by (b) (4), DVM, PhD, DACVP (page 399 and 414).

Histological Findings

Few histopathological findings were observed in animals euthanized at the scheduled sacrifice on Day 15. Group 2 and 4 animals that died or were sacrificed early had histopathological findings that included mild to moderate degeneration of the tubules in the kidneys in F, mild to moderate lymphoid depletion of the white pulp in the spleen, and minimal to moderate lymphoid necrosis in the lymph nodes (mandibular and mesenteric), thymus and Peyer's patch. The findings in these animals were more severe in F.

Summary table of selected microscopic findings

Tissue	Finding	Group	MALE (n=10*)					FEMALE (n=10*)				
			1	2	3	4	5	1	2	3	4	5
Eye	Retinal Dysplasia	minimal:	0	0	-	1	0	0	0	-	0	0
		mild:	0	0	-	0	0	0	0	-	(1)	0
Heart	Cardiomyopathy	minimal:	2	3	-	4	3	0	2	-	0	0
		Mixed cell infiltration	minimal:	0	1 (1)	-	0	0	0	1	-	0
Liver	Hemorrhage	minimal:	0	0	0/1	0	0	0	0	-	0	0
		mild:	0	0	1/1	0	0	0	0	-	0	0
	Mononuclear cell Infiltration	minimal:	2	5	0/1	1	0	1	0	-	0	0
		Hepatocellular necrosis	minimal:	0	1	0/1	0	0	0	0	-	(1)
	Hepatocellular vacuolation	mild:	0	0	1/1	0	1	0	0	-	0	0
		minimal:	0	0	0/1	0	0	0	0	-	1	0
	Hepatocellular regeneration	minimal:	0	0	0/1	0	0	0	1	-	0	0
		minimal:	0	0	0/1	0	0	0	1	-	0	0
Lungs	Histiocytosis	minimal:	0	0	-	1	0	3	0	-	0	0
		Fibrosis	minimal:	0	0	-	0	0	0	0	-	0
	Mononuclear cell Infiltration	mild:	0	0	-	1	0	0	0	-	0	0
		minimal:	0	0	-	1	0	0	0	-	0	0
	Congestion	minimal:	0	0	-	0	0	0	0	-	0	0
		mild:	0	0	-	0	0	0	0	-	0	0
moderate:		0	(1)	-	0	0	0	0	-	(1)	0	
Kidney	CPN	minimal:	3	3 (1)	-	3	3	2	2	0/1	2	2
		mild:	0	0	-	2	0	0	0	0/1	0	0
	Pelvic dilation	minimal:	1	0	-	0	0	1	0	0/1	0	0
		mild:	1	1	-	0	0	0	0	1/1	0	1
		moderate:	0	0	-	0	0	1	0	0/1	0	0
	Mononuclear cell infiltration	minimal:	0	0	-	0	0	0	0	0/1	0	0
		mild:	0	0	-	0	0	0	0	0/1	0	1

Tissue	Finding	Group	MALE (n=10*)					FEMALE (n=10*)				
			1	2	3	4	5	1	2	3	4	5
Kidney	Tubular degeneration	minimal:	0	0	-	0	0	0	0	0/1	0	0
		mild:	0	0	-	0	0	0	0	0/1	(2)	0
		moderate:	0	0	-	0	0	0	(3)	0/1	(3)	0
Esophagus	Hemorrhage	minimal:	0	0	-	0	1	0	0	-	0	0
		Myofiber regeneration	minimal:	6	6	-	2	2	5	3	-	2
		mild:	0	2	-	1	1	2	4	-	0	3
	Myofiber necrosis	minimal:	0	(1)	-	0	0	0	0	-	(1)	0
		Fibrosis	minimal:	0	4	-	2	1	2	3	-	2
		mild:	2	1	-	1	0	0	3	-	0	4
Stomach	Hemorrhage	minimal:	0	0	-	0	0	0	(2)	-	0	0
Pancreas	Acinar cell atrophy	minimal:	0	0	-	0	1	0	0	-	0	0
Spleen	Depleted white pulp	minimal:	0	0	-	0	0	0	0	-	0	0
		mild:	0	(1)	-	0	0	0	(2)	-	(2)	0
		moderate:	0	0	-	0	0	0	(1)	-	(3)	0
Thymus	Hemorrhage	minimal:	5	3	1/2	3	2	3	4	1/1	2 (1)	1
		Lymphoid necrosis	minimal:	0	0	0/2	0	0	0	0	0/1	0
		mild:	0	(1)	0/2	0	0	0	0	0/1	(1)	0
		moderate:	0	0	0/2	0	0	0	(3)	0/1	(4)	0
Peyers Patch	Lymphoid necrosis	minimal:	0	0/8	-	0	0/8	0	(2)	-	(1/3)	0
		mild:	0	0/8	-	0	0/8	0	(1)	-	(1/3)	0
	Mineralization	minimal:	0	0/8	-	0	1/8	0	0	-	0/4	0
Mandibular Lymph Node	Hemorrhage	minimal:	1	0	-	1	4	1	(1)	-	(1)	1
		mild:	0	0	-	0	0	0	0	-	(1)	0
	Fibrosis	minimal:	0	0	-	0	0	0	0	-	0	0
		mild:	1	0	-	0	0	0	0	-	0	0
	Neutrophilic inflammation	minimal:	0	0	-	0	0	0	0	-	0	0
		mild:	1	0	-	0	0	0	0	-	0	0
	Follicular Hyperplasia	minimal:	0	0	-	0	0	0	0	-	0	0
		mild:	0	0	-	0	0	0	0	-	0	0
		moderate:	2	1	-	2	2	0	3	-	4	2
	Plasmacytosis	minimal:	0	0	-	0	0	0	0	-	0	0
		mild:	0	0	-	0	0	0	0	-	0	0
		moderate:	1	0	-	3	2	0	3	-	3	1
	Lymphoid necrosis	minimal:	0	0	-	0	0	0	0	-	0	0
mild:		0	(1)	-	0	0	0	(3)	-	(5)	0	

Tissue	Finding	Group	MALE (n=10*)					FEMALE (n=10*)				
			1	2	3	4	5	1	2	3	4	5
Mesenteric Lymph Node	Hemorrhage	minimal:	0	(1)	-	0	2	2	(2)	-	(3)	0
		Lymphoid necrosis	minimal:	0	0	-	0	0	0	(1)	-	0
	mild:	0	(1)	-	0	0	0	(2)	-	(3)	0	
	moderate:	0	0	-	0	0	0	0	-	(1)	0	

Groups: 1 - Placebo, 2 – Fresh nimodipine (120/90/45 mg/kg/day), 3 – Aged nimodipine (60/30 mg/kg/day), 4 – (120/90/45 mg/kg/day) Aged nimodipine (60/30 mg/kg/day), and 5 - (b) (4)
 CPN- Chronic progressive nephropathy; findings in animals found dead or sacrificed moribund are in parenthesis (1 M and 3 F for group 2 and 5 F group 4). *n=10 unless otherwise indicated for Group 3, as incidence/№ of animals.

11 Integrated Summary and Safety Evaluation

Nimotop® (nimodipine) is approved for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms, regardless of the patient's post-ictus neurological condition (i.e., Hunt and Hess Grades I-V). Nymalize® is an oral version of nimodipine. Nimodipine is an L-type calcium channel blocker.

During the review process, the CMC reviewer identified degradants in drug product batches with stability specification limits that were above the qualification threshold. In order to address this concern, the Sponsor conducted a 14-day toxicology study in rats with an aged nimodipine batch that had higher levels of the degradants and a (b) (4) batch.

In the 14-day toxicology study, fresh nimodipine, aged nimodipine, and (b) (4) were administered (b.i.d. initially) to rats for 14 Days. The HD of fresh and aged nimodipine were lethal; deaths occurred in a M rat on Day 2 at 120 mg/kg/day (after 2 doses at 60 mg/kg and 1 dose at 45 mg/kg) and in F rats at 90 mg/kg/day on Day 2 (after 2 doses at 45 mg/kg). The dose was reduced to 45 mg/kg b.i.d. in M on Day 2 because of the adverse clinical sign of distended abdomen; dosing was started at 45 mg/kg b.i.d. for F on Day 1. Administration of HD fresh and aged nimodipine was further reduced to 45 mg/kg/day on Day 3 for M and Day 2 for F, by changing to q.d. dosing from b.i.d., due to mortality of 3 and 5 F in the fresh and aged nimodipine groups respectively. Clinical signs primarily observed in animals that were euthanized moribund included decreased activity, hypothermia, slow breathing, partially closed eyelids, and wobbly gait. The Sponsor considered toxic effects on the kidney the likely cause of death or moribund condition because of the microscopic findings of mild to moderate degeneration of the tubules that correlated with increases in serum urea nitrogen and creatinine in individual animals. Other clinical findings included fecal stain, soft stools, diarrhea and urine stain; however, incidences of these findings occurred in all groups and were generally similar between animals treated with fresh (Group 2) and aged (Group 4) nimodipine batches. Occurrences of fecal stain, soft stools, diarrhea, and urine stain were only observed sporadically from Days 4-15 in M and Days 3-15 in

F, after the reduction of dose to 45 mg/kg/day. Clinical signs in M or F administered (b) (4) (b) (4) (b) (4) were observed primarily on Days 14 or 15, and consisted of soft stools, fecal stain, and red pinna(e)/extremities. Decreased body weight gains of greater than 10% occurred with treatment of HD fresh and aged nimodipine in M and (b) (4) (b) (4) in M and F. The greatest change in body weight gain was observed in animals administered (b) (4). Changes in food consumption did not account for the decreased body weight gain. The major changes in hematology and biochemical parameters were observed in animals from Groups 2 and 4 that were sacrificed moribund on Day 2. Animals that survived to Day 15 generally had changes that were small or similar to animals administered fresh nimodipine, apart from biochemical changes in animals administered (b) (4) (b) (4) that included increases in globulin, glucose, urea nitrogen, and creatinine, and decreases in triglycerides, albumin, A/G ratio, and calcium

A statistically significant increase was observed in relative mean M and F heart weight and relative mean F liver weight treated with HD fresh and aged nimodipine that was similar in magnitude. A statistically significant small increase in relative mean lung weight was only observed in HD aged nimodipine treated animals; however, animals treated with HD fresh nimodipine also had a small increase in relative mean lung weight. No histopathological findings that correlated with the increases in organ weights were observed and few histopathological findings were observed in animals euthanized on Day 15. Histopathological findings in animals that died or were sacrificed early included mild to moderate degeneration of the tubules in the kidneys in F, mild to moderate lymphoid depletion of the white pulp in the spleen, and minimal to moderate lymphoid necrosis in the lymph nodes (mandibular and mesenteric), thymus and Peyer's patch, suggesting an effect in the kidneys and lymphoid organs.

The main target organs for nimodipine in animals that died prematurely appeared to be the kidney and lymphoid organs, with moribund animals having degeneration of the tubules that correlated with increases in serum urea nitrogen and creatinine, and signs of lymphoid depletion and necrosis. The severity of the toxic effects appeared similar between the fresh and aged batches of nimodipine, suggesting that the degradants did not have an additional toxic effect. Animals treated with 45 mg/kg/day of fresh or aged nimodipine had few toxic findings, further suggesting that the degradants did not have any additional toxic effects. In conclusion, in the 14-day study of nimodipine (fresh and degraded), there was no substantial difference between the groups treated with fresh or aged nimodipine, suggesting that the impurities 1-4 and (b) (4) (b) (4) did not cause any further toxicity.

In animals treated with 45 mg/kg/day of aged nimodipine, the daily doses (based on body surface area) of the impurities 1-4, and (b) (4) (b) (4) were equal or greater than that expected with the recommended human dose at the Sponsor's stability specification. As toxicity findings were similar to animals treated with the fresh nimodipine, these degradants are qualified.

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/s/

RICHARD J SIAREY
07/13/2012

LOIS M FREED
07/13/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203-340 **Applicant:** Arbor Pharmaceuticals **Stamp Date:** 18th Nov 2011

Drug Name: Nymalize® **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			There is no Pharmacology/Toxicology section.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			n/a
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			n/a
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			No IND studies were required, although the Sponsor was informed that additional safety studies may be needed, if any safety concerns arose (e.g., impurities, degradants).
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			n/a
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			n/a
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			n/a

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		Labeling has been taken from the Nimotop® (RLD) labeling.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		This will be a matter for review.
11	Has the applicant addressed any abuse potential issues in the submission?		√	n/a
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		√	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Yes. From a pharmacology/toxicology perspective the NDA is fileable. The Sponsor has not submitted any nonclinical data and relies on the Nimotop® label. However, if the safety concerns CMC has with a number of impurities are not addressed, then additional nonclinical studies will be needed.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The drug product stability specification provided in the original NDA submission provides for acceptance criteria for 6 specified impurities that exceed the ICH qualification threshold (0.2%).

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/s/

RICHARD J SIAREY
02/24/2012

LOIS M FREED
02/24/2012