CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203340Orig1s000

CHEMISTRY REVIEW(S)

M E M O R A N D U M

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

DATE: March 19, 2013

FROM: Donghao (Robert) Lu, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 203-340

SUBJECT: OC recommendation

RECOMMENDATION: The drug product, Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL, is recommended for approval from a CMC perspective – an overall "Acceptable" recommendation from the Office of Compliance is received.

REVIEW NOTE:

The NDA 203-340 CMC review was completed. All other CMC issues have been resolved, except the pending overall recommendation from the Office of Compliance (OC) on manufacturing facilities. We have now received the OC "Acceptable" overall recommendation. The EES summary report is shown below.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203340/000	**Sponsor:**	ARBOR PHARMS INC
Org. Code:	120		980 HAMMOND DR STE 1250
Priority:	3		ATLANTA, GA 30115
Stamp Date:	18-NOV-2011	**Brand Name:**	NIMODIPINE.
PDUFA Date:	20-MAY-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	NIMODIPINE.
District Goal:	19-MAR-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION; NIMODIPINE; 60MG/20ML

FDA Contacts:	T. BOUIE	Project Manager		3017961649
	D. LU	Review Chemist	(HFD-150)	3017962059
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	ACCEPTABLE	on 19-MAR-2013	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 14-JAN-2013	by EES_PROD		
	PENDING	on 14-JAN-2013	by EES_PROD		
	PENDING	on 14-JAN-2013	by EES_PROD		
	PENDING	on 07-NOV-2012	by EES_PROD		
	WITHHOLD	on 22-MAY-2012	by EES_PROD		
	PENDING	on 09-MAR-2012	by EES_PROD		
	PENDING	on 17-JAN-2012	by EES_PROD		
	PENDING	on 13-DEC-2011	by EES_PROD		
	PENDING	on 13-DEC-2011	by EES_PROD		
	PENDING	on 13-DEC-2011	by EES_PROD		

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-MAR-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: (b) (4) LIQUID (OTHER THAN SUSP & EMULSIONS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: (b) (4) API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-FEB-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	(b) (4) IQUID (OTHER THAN SUSP & EMULSIONS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-JAN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

DONGHAO R LU
03/19/2013

RAMESH K SOOD
03/19/2013

NDA 203-340

(Review #2)

Nymalize (Nimodipine)
Oral Solution
60 mg/20 mL

Arbor Pharmaceuticals, Inc.

Division of Neurology Drug Products

Donghao (Robert) Lu, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-340
2. REVIEW NUMBER: 2
3. REVIEW DATE: 6 AUGUST, 2012
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE
NDA 203-340	18-NOV-2011
NDA 203-340 (Amendment 001, name) (DMETS)	21-NOV-2011
NDA 203-340 (Amendment 002, impurity)	10-JAN-2012
NDA 203-340 (Amendment 003, protocol)	10-FEB-2012
NDA 203-340 (Amendment 004, labeling)	17-FEB-2012
NDA 203-340 (Amendment 005, stability)	6-MAR-2012
NDA 203-340 (Amendment 006, labeling)	27-MAR-2012
NDA 203-340 (Amendment 007, IR responses)	30-MAR-2012
NDA 203-340 (Amendment 008, packaging)	19-APR-2012

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 203-340 (Amendment 009, specification)	30-APR-2012
NDA 203-340 (Amendment 010, stability)	4-MAY-2012
NDA 203-340 (Amendment 014, labeling)	25-MAY-2012
NDA 203-340 (Amendment 015, micro)	22-JUNE-2012
NDA 203-340 (Amendment 016, labeling)	29-JUNE-2012
NDA 203-340 (Amendment 017, labeling)	16-JULY-2012
NDA 203-340 (Amendment 018, specification)	1-AUG-2012

7. NAME & ADDRESS OF APPLICANT:

NAME:	**Arbor Pharmaceuticals Inc.**
ADDRESS:	**980 Hammond Drive, Suite 1250 Atlanta, GA 30328**
REPRESENTATIVE:	**Allison Lowry, Director, Quality & Regulatory Affairs, P: 678-334-2428**

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**Nymalize (Nimodipine)**
NON-PROPRIETARY NAME (USAN)	**Nimodipine**
CODE NAME/ NUMBER (ONDC ONLY)	
CHEMISTRY TYPE / SUBMISSION PRIORITY	**3P**

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: Calcium channel blocker

11. DOSAGE FORM: Oral solution

12. STRENGTH/POTENCY: 60 mg/20 mL

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: _x_ R_x ___OTC

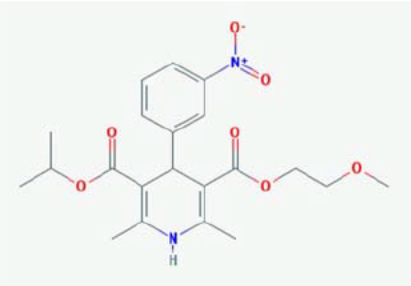
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): Nimodipine
Name (USP): Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate
Other Name: 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid, 2-methoxyethyl, 1-methylethyl ester 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine

(CAS) Registry Num: 66085-59-4

Structural Formula:



Mol. Formula: $C_{21}H_{26}N_2O_7$
Mol. Wt.: 418.44

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	II	(b) (4)		3	Adequate	28-Feb-2012
	III			3	Adequate	28-Feb-2012
	III			3	Adequate	28-Feb-2012
	III			3	Adequate	28-Feb-2012
	III			3	Adequate	28-Feb-2012
	III			3	Adequate	28-Feb-2012

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	No validation request	12-APR-12	Donghao Lu, Ph.D.
OSE DMEPA	Acceptable	26-JUN-12	Jung Lee, RPh
EA	Acceptable	11-FEB-12	Donghao Lu, Ph.D.
Biopharm	Acceptable	24-APR-12	Kareen Riviere, Ph.D.
Pharm/Tox	Acceptable	13-JULY-12	Richard J. Siarey, Ph.D.
Micro Consultation	Acceptable	28-JUN-12	Erika Pfeiler, Ph.D.

The Chemistry Review for NDA 203-340

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The review covers the amendments received through 8/1/2012 (also see the previous review on NDA and early amendments). The drug product, Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL, is recommended as APPROVABLE from a CMC perspective, pending Office of Compliance's recommendation. A final memorandum will be submitted when the pending recommendation is received.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is nimodipine. The chemical name is isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate. It has a molecular formula of $C_{21}H_{26}N_2O_7$ and its molecular weight is 418.44. Nimodipine was approved in 1988 with another NDA as Nimotop® capsules (NDA 18-869, 1988). There are also several generic capsule products approved in USA. USP monograph of nimodipine drug substance was established.

Nimodipine is a light yellow or yellow crystalline powder. The melting point is between (b) (4) and (b) (4) °C. It is practically insoluble in water but freely soluble in ethyl acetate and sparingly soluble in ethanol. The drug substance is obtained from (b) (4). The manufacture of nimodipine drug substance was described in Type II DMF (b) (4) from (b) (4). The DMF was reviewed in August 3, 2006 by Dr. Shankar Saha at FDA/OGD and determined to be acceptable to support an ANDA for nimodipine capsules. The information submitted after Dr. Saha's review is further reviewed and found adequate to support this NDA.

Limited CMC information on nimodipine drug substance was provided in this NDA. The nimodipine drug substance from (b) (4) is packaged in (b) (4), inside a (b) (4), all individually sealed, and placed (b) (4). The drug substance specification was provided. The batch analysis data for two drug substance batches (manufactured in September 2009 and May 2011, respectively) were provided and found adequate.

2. Drug Product

The drug product is Nymalize (nimodipine) oral solution, 60 mg/20 mL. It is intended for oral administration. Nymalize (nimodipine) oral solution is a pale yellow liquid containing 60 mg/20 mL of nimodipine. The product contains (b) (4) polyethylene glycol 400, ethyl alcohol and glycerin (b) (4) The sponsor submitted a request to waive the requirement for the submission of evidence measuring the in vivo bioavailability of Nimodipine oral solution per 21 C.F.R. 320.22 (b) (3). The biopharm reviewer accepted the biowaiver request.

The manufacturing process for nimodipine oral solution was described. (b) (4) . The product is packaged in (b) (4) 16 ounce bottles

with (b) (4) white (b) (4) caps with (b) (4) induction seal foil liners and also packaged in (b) (4) mL HDPE unit-dose cups with (b) (4) lidding (foil stock heat sealing).

The sponsor requested a (b) (4) month of expiration date for the bottle and unit dose packaging. However, based on the impurity profile and the pharm/tox evaluation on the preclinical data, a 9 month of expiration date for the bottle and unit dose packaging is recommended.

B. Description of How the Drug Product is Intended to be Used

Nimodipine oral solution drug product contains the calcium channel blocker indicated to improve neurological outcome in patients with subarachnoid hemorrhage (SAH) due to ruptured aneurysms. Oral nimodipine liquid-filled gelatin capsules (Nimotop) were FDA-approved and have been on the US market since 1988. Medication errors occurred due to inadvertent intravenous administration of the extraction from the capsules for patients who cannot swallow the capsule and thus take the extracted medicine through a nasogastric tube. The new oral solution product is developed to minimize such medication errors.

The recommended dosing of nimodipine oral solution is 20 mL (60 mg) every 4 hours for 21 consecutive days. Nimodipine oral solution is preferably administered not less than one hour before or two hours after meals. The products should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF). The products should be protected from light and should be not stored in refrigerator. A 9 month of expiration date for the bottle and unit dose packaging is recommended.

C. Basis for Approvability or Not-Approval Recommendation

Arbor has submitted adequate CMC information to support this NDA. All the remaining issues have been adequately addressed by the applicant. However, Office of Compliance's recommendation on manufacturing facilities has not been received.

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

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/s/

DONGHAO R LU
08/08/2012

RAMESH K SOOD
08/08/2012

M E M O R A N D U M

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

DATE: August 8, 2012

FROM: Donghao (Robert) Lu, Ph.D.
Division of Pre-Marketing Assessment - I
Office of New Drug Quality Assessment

TO: File NDA 203-340

SUBJECT: OC recommendation

RECOMMENDATION: The drug product, Nymalize (Nimodipine) Oral Solution, 60 mg/20 mL, can not be recommended for approval from a CMC perspective because of an overall "Withhold" recommendation from the Office of Compliance.

REVIEW NOTE:

The NDA 203-340 CMC review was completed. All other CMC issues have been resolved, except one pending issue on the overall recommendation from the Office of Compliance (OC) on manufacturing facilities. We have now received the OC withhold recommendation (below) on one of the facilities, i.e. Enterprises Importfab in Pointe Claire, Quebec, Canada.

From: Gould, Shawn
Sent: Wednesday, August 08, 2012 2:19 PM
To: Heimann, Martha R; Dunn, Billy; Kishore, Vandna N; Lu, Donghao; Sood, Ramesh
Cc: CDER OMPQ REVIEW; Smith, Derek; Katz, Russell G; Gooen, Tara
Subject: RE: NDA 203340 Nimodipine oral solution-Nymalize-SAH-OC question

Agreed. The facility in question is Enterprises Importfab in Pointe Claire, Quebec. EES already has a withhold recommendation as of May 22, 2012 and will not be changing soon.

/srg

The Establishment Evaluation Report summary is shown on the next pages.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 203340/000	**Sponsor:**	ARBOR PHARMS INC
Org. Code:	120		980 HAMMOND DR STE 1250
Priority:	3		ATLANTA, GA 30328
Stamp Date:	18-NOV-2011	**Brand Name:**	NIMODIPINE.
PDUFA Date:	18-MAY-2012	**Estab. Name:**	
Action Goal:		**Generic Name:**	NIMODIPINE.
District Goal:	19-MAR-2012	**Product Number; Dosage Form; Ingredient; Strengths**	001; SOLUTION; NIMODIPINE; 60MG/20ML

FDA Contacts:	T. BOUIE	Project Manager		3017961649
	D. LU	Review Chemist	(HFD-150)	3017962059
	M. HEIMANN	Team Leader		3017961678

Overall Recommendation:	WITHHOLD	on 22-MAY-2012	by EES_PROD
	PENDING	on 09-MAR-2012	by EES_PROD
	PENDING	on 17-JAN-2012	by EES_PROD
	PENDING	on 13-DEC-2011	by EES_PROD
	PENDING	on 13-DEC-2011	by EES_PROD
	PENDING	on 13-DEC-2011	by EES_PROD

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-MAR-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER		
Profile:	LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS,	**OAI Status:**	POTENTIAL OAI
Last Milestone:	UNDER REVIEW		
Milestone Date:	17-FEB-2012		

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE PACKAGER DRUG SUBSTANCE RELEASE TESTER		
Profile:	(b) (4) API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-FEB-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-DEC-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS,	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-JAN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	INSPECTION PERFORMED		
Milestone Date:	01-MAY-2012		

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/s/

DONGHAO R LU
08/08/2012

RAMESH K SOOD
08/08/2012

Nymalize (Nimodipine)
Oral Solution
60 mg/20 mL

Arbor Pharmaceuticals, Inc.

Division of Neurology Drug Products

Donghao (Robert) Lu, Ph.D.
Division I of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-340
2. REVIEW NUMBER: 1
3. REVIEW DATE: 16 APRIL 2012
4. REVIEWER: Donghao (Robert) Lu, Ph.D.
5. PREVIOUS DOCUMENTS:

PREVIOUS DOCUMENTS	DOCUMENT DATE

6. SUBMISSION(S) BEING REVIEWED:

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 203-340	18-NOV-2011
NDA 203-340 (Amendment 001, name) (DMETS)	21-NOV-2011
NDA 203-340 (Amendment 002, impurity)	10-JAN-2012
NDA 203-340 (Amendment 003, protocol)	10-FEB-2012
NDA 203-340 (Amendment 004, labeling)	17-FEB-2012
NDA 203-340 (Amendment 005, stability)	6-MAR-2012
NDA 203-340 (Amendment 006, labeling)	27-MAR-2012
NDA 203-340 (Amendment 007, IR responses)	30-MAR-2012
NDA 203-340 (Amendment 008, packaging)	19-APR-2012

7. NAME & ADDRESS OF APPLICANT:

NAME:	Arbor Pharmaceuticals Inc.
ADDRESS:	980 Hammond Drive, Suite 1250 Atlanta, GA 30328
REPRESENTATIVE:	Allison Lowry, Director, Quality & Regulatory Affairs, P: 678-334-2428

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	**Nymalize (Nimodipine)**
NON-PROPRIETARY NAME (USAN)	**Nimodipine**
CODE NAME/ NUMBER (ONDC ONLY)	
CHEMISTRY TYPE / SUBMISSION PRIORITY	**3P**

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: Calcium channel blocker

11. DOSAGE FORM: Oral solution

12. STRENGTH/POTENCY: 60 mg/20 mL

13. ROUTE OF ADMINISTRATION: Oral

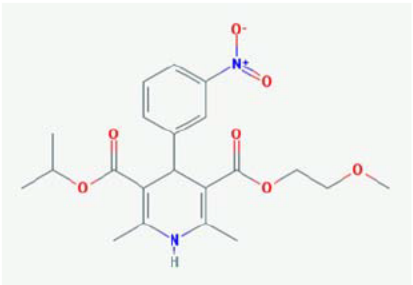
14. R_x/OTC DISPENSED: _x_ R_x ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): Nimodipine
Name (USP): Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate
Other Name: 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid, 2-methoxyethyl, 1-methylethyl ester 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine
(CAS) Registry Num: 66085-59-4

Structural Formula:



Mol. Formula: $C_{21}H_{26}N_2O_7$
Mol. Wt.: 418.44

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)		(b) (4)		1	Adequate	28-Feb-2012
				1	Adequate	28-Feb-2012
				1	Adequate	28-Feb-2012
				1	Adequate	28-Feb-2012
				1	Adequate	28-Feb-2012
				1	Adequate	28-Feb-2012

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A: There is enough data in the application, therefore the DMF did not need to be reviewed.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	No validation request	12-APR-12	Donghao Lu, Ph.D.
OSE DMEPA	Acceptable	1-MAR-12	Jung Lee, RPh
EA	Acceptable	11-FEB-12	Donghao Lu, Ph.D.
Biopharm	Acceptable	24-APR-12	Kareen Riviere, Ph.D.
Pharm/Tox	Pending		
Micro Consultation	Pending		

The Chemistry Review for NDA 203-340

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The review includes the evaluation of CMC information provided in the original NDA and amendments received through 4/19/2012. From a CMC perspective, the application can not be recommended for approval at this time. Refer to Section C for a summary of outstanding issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substance is nimodipine. The chemical name is isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate. It has a

molecular formula of $C_{21}H_{26}N_2O_7$ and its molecular weight is 418.44. Nimodipine was approved in 1988 with another NDA as Nimotop® capsules (NDA 18-869, 1988). There are also several generic capsule products approved in USA. USP monograph of nimodipine drug substance was established.

Nimodipine is a light yellow or yellow crystalline powder. The melting point is between (b) (4) and (b) (4) °C. It is practically insoluble in water but freely soluble in ethyl acetate and sparingly soluble in ethanol. The drug substance is obtained from (b) (4). The manufacture of nimodipine drug substance was described in Type II DMF (b) (4). The DMF was reviewed in August 3, 2006 by Dr. Shankar Saha at FDA/OGD and determined to be acceptable to support an ANDA for nimodipine capsules. The information submitted after Dr. Saha's review is further reviewed and found adequate to support this NDA.

Limited CMC information on nimodipine drug substance was provided in this NDA. The nimodipine drug substance from (b) (4). is (b) (4) (b) (4) placed into a (b) (4). The drug substance specification was provided. The batch analysis data for two drug substance batches (manufactured in September 2009 and May 2011, respectively) were provided and found adequate.

2. Drug Product

The drug product is Nymalize (nimodipine) oral solution, 60 mg/20 mL. It is intended for oral administration. Nymalize (nimodipine) oral solution is a pale yellow liquid containing 60 mg/20 mL of nimodipine. The product contains (b) (4) polyethylene glycol 400, ethyl alcohol and glycerin (b) (4) (b) (4). The sponsor submitted a request to waive the requirement for the submission of evidence measuring the in vivo bioavailability of Nimodipine oral solution per 21 C.F.R. 320.22 (b) (3). The biopharm review accepted the biowaiver request.

The manufacturing process for nimodipine oral solution was described. (b) (4) (b) (4) (b) (4). The product is packaged in (b) (4) high density polyethylene 16 ounce bottles with (b) (4) white (b) (4) caps with (b) (4) induction seal foil liners and also packaged in (b) (4) mL HDPE unit-dose cups with (b) (4) (b) (4).

The sponsor requested a (b) (4) month of expiration date for the bottle and unit dose packaging. However, the CMC recommendation on the expiration date is pending the pharm/tox review on allowable impurity levels.

B. Description of How the Drug Product is Intended to be Used

Nimodipine oral solution drug product contains the calcium channel blocker indicated to improve neurological outcome in patients with subarachnoid hemorrhage (SAH) due to ruptured aneurysms. Oral nimodipine liquid-filled gelatin capsules (Nimotop) were FDA-approved and have been on the US market since 1988. Medication errors occurred due to inadvertent intravenous administration of the extraction from the capsules for patients who cannot swallow the capsule and thus take the extracted medicine through a nasogastric tube. The new oral solution product is developed to minimize such medication errors.

The recommended dosing of nimodipine oral solution is 20 mL (60 mg) every 4 hours for 21 consecutive days. Nimodipine oral solution is preferably administered not less than one hour before or two hours after meals. The products should be stored at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF). The products should be protected from light and should be not stored in refrigerator. The recommendation of the expiration period (shelf life) of the products is pending the pharm/tox evaluation.

C. Basis for Approvability or Not-Approval Recommendation

Arbor has submitted adequate information to address a number of CMC deficiencies. The following issues have not been adequately addressed by the applicant or are pending reviews from other disciplines. Addendum to the review will be entered into DARRTS to address the following issues:

Compliance – pending

Drug Product Specification
Specific identification test method – proposed but not submitted for review
Impurities above qualification threshold – pending receipt of supporting toxicity data and review by Pharm/Tox
Difference in impurity specs between cup and bottle – pending receipt of revision
Use of detector wavelength for impurity test – pending receipt of supporting toxicity data

Micro Consultation
Deficiencies were sent 3/22 – pending response from applicant and micro recommendation

Stability
Photostability results – pending
Expiry – pending Pharm/Tox acceptance of impurity specs

Labeling
Shake well statement – pending receipt of additional information

III. Administrative

A. Reviewer's Signature

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

58 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

DONGHAO R LU
05/11/2012

MARTHA R HEIMANN
05/11/2012
Signed for Dr. Ramesh Sood.

I concur with Dr. Lu's recommendation

Initial Quality Assessment
Branch I
Division of New Drug Quality Assessment I

OND Division:	Division of Neurology Products
NDA:	203-340
Applicant:	Arbor Pharmaceuticals
Stamp Date:	18-Nov-2011
PDUFA Date:	To be determined
Trademark:	Nymalize is proposed
Established Name:	Nimodipine
Dosage Form:	Solution
Route of Administration:	Oral
Indication:	Subarachnoid hemorrhage
CMC Lead:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	The application is considered minimally fileable for CMC.	
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

Summary

Nimodipine is a calcium channel blocker that was originally developed and marketed by Bayer Pharmaceuticals as a 30 mg soft gelatin capsule under NDA 18-869 (approved 1988). It is indicated for improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms. Bayer discontinued marketing of the product in 2009; however, generic versions are marketed by three firms.

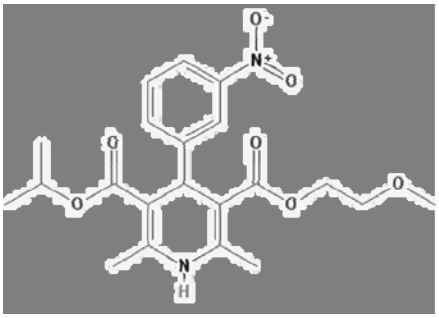
The recommended dose of nimodipine is 60 mg (2 capsules) every 4 hours for 21 consecutive days. Therapy should be initiated within 96 hours of the subarachnoid hemorrhage. For patients who cannot swallow the capsule, the label instructs that the contents of the capsule be withdrawn using a syringe equipped with an 18 gauge needle. The drug is then administered via a naso-gastric tube and washed down the tube with 30 mL of normal saline. This has resulted in a number of medication errors, some fatal, due to inadvertent intravenous administration. To address this concern, the Agency had encouraged Bayer, and later the generic firms, to develop a liquid formulation.

The current NDA provides for an oral solution containing 60 mg/mL of nimodipine in a PEG-400/glycerin based vehicle. The product was developed by (b) (4) and acquired by Arbor Pharmaceuticals just prior to submission of the application. During development, (b) (4) sought via a pre-IND meeting that was originally scheduled for 30-Mar-2011. The meeting was cancelled by the firm after receipt of preliminary comments. In

the preliminary comments, the firm was advised that the recommended stability data package is 12 months long-term and 6 months accelerated data but that submission of less data would not be a reason to refuse-to file. The firm was also advised that additional stability data received after mid-cycle might not be reviewed in the same review cycle. The firm was also advised by the Agency 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."*

Drug Substance

The active ingredient, nimodipine [chemical name: 1,4-dihydro-2,6-dimethyl- 4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid, 2-methoxyethyl 1-methylethyl ester], is a well characterized small molecule with molecular formula $C_{21}H_{26}N_2O_7$ and molecular weight 418.44. The chemical structure of nimodipine is:



The bulk drug substance is a light yellow or yellow crystalline powder, with melting point between (b) (4) and (b) (4)C. Nimodipine is freely soluble in ethyl acetate, sparingly soluble in ethanol 96%, and practically insoluble in water.

The bulk drug substance is manufactured (b) (4). All information regarding the manufacture and control of the drug substance in incorporated by reference to the manufacturer's DMF No (b) (4). The DMF was most recently reviewed on 27-Jul-2006 and found adequate. The DMF has been updated since the last review and was resubmitted in CTD format on 22-Nove-2010. Therefore, the DMF should be reviewed.

Information in the NDA itself is limited to the information summarized above. The applicant references the current Nimodipine, USP monograph for the acceptance specification and analytical procedures.

Drug Product

The proposed dosage form is a solution for oral administration containing 60 mg/20 mL of nimodipine. The components and composition of Nimodipine Oral Solution are summarized in the applicant's **Table 1** [Module 3.2.P.1]. All excipients are compendial and have been previously used in oral dosage forms.

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)	NF	(b) (4)		
Nimodipine		USP			
Ethyl alcohol (b) (4)		USP			
Methylparaben		NF			
Purified Water		USP			
Sodium Phosphate Monobasic Monohydrate		USP			
Sodium Phosphate Dibasic Dihydrate		USP			
Glycerin		USP			
Polyethylene Glycol 400		NF			

The drug product will be packaged in 16 ounce HDPE bottles with (b) (4) closures and HSL-1 induction seal foil liners. The product will also be packaged in HDPE unit-dose cups with (b) (4) lidding.

Nimodipine Oral Solution will be manufactured and packaged in 16 ounce bottles by Importfab, Pointe-Claire QC, Canada. The product will be repackaged into 20 mL unit-dose cups by (b) (4). The manufacturing process is straightforward and involves (b) (4)

The pharmaceutical development report presents a traditional, empirical, approach to formulation and manufacturing process development.

In Module 3.2.P.5.1 the applicant presents the Quality Control Specifications outlined in applicant's **Table 1** and **Table 2** below.

Table 1: Quality Control Specifications, 16 ounce bottle

Test	Acceptance Criteria	Regulatory Analytical Procedure
Identification	(b) (4) nimodipine; retention time corresponds to that of RS	NPLC-1266
pH	6.0-7.0	NPPF-191
Assay for Nimodipine	(b) (4) LC	NPLC-1266
Assay for Methylparaben	LC	NPLC-1267
Assay for Impurities: (b) (4)	NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT	NPLC-1266
Appearance/Description	(b) (4)	Organoleptique
Weight of Filled, Capped and Labeled Bottle		USP
Density		USP
Microbial Limits Testing:		
Total aerobic plate count	NMT (b) (4)	USP / NPMI-242
Total mold & yeast	NMT	USP / NPMI-242
Escherichia coli	Negative	USP / NPMI-242
Salmonella species	Negative	USP / NPMI-242
Staphylococcus aureus	Negative	USP / NPMI-242
Pseudomonas aeruginosa	Negative	USP / NPMI-242

Table 2: Quality Control Specifications, (b) (4) mL cup

Test	Acceptance Criteria	Regulatory Analytical Procedure
Identification	(b) (4) nimodipine; retention time corresponds to that of RS	NPLC-1266
Appearance/Description	(b) (4)	Organoleptique
Filled HDPE Cup with Foil Seal	NLT (b) (4)	USP

On further examination of the application, the "Stability Specification" was located in Module 3.2.P.8.1 (p. 14). The Stability Specification, which is shown in applicant's **Table 13** on the following page, provides for (b) (4) limits for related substances.

Table 13: Stability Specifications, 16 ounce bottle and (b) (4) mL unit-dose cup

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) caps (b) (4) (b) (4) mL HDPE (b) (4) Cup (b) (4) (b) (4) id.	Visual
Identification	(b) (4) nimodipine; retention time corresponds to that of RS	NPLC-1266
pH	(b) (4)	NPPF-191
Assay for Nimodipine	LC	NPLC-1266
Assay for Methylparaben	LC	NPLC-1267
Assay for Impurities: (b) (4)	NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT	NPLC-1266
(b) (4)	Reports	Gravimetric
Antimicrobial Effectiveness Testing	Passes test	USP / NPMI-243

The proposed limits for the specified impurities exceed the ICH identification and qualification threshold (b) (4) % for the proposed (b) (4) mg daily dose of nimodipine). The applicant has not identified five of the specified impurities or provided any justification for the proposed limits. With respect to unidentified impurities, the applicant indicates in Module 3.2.P.5. that *"Overall, stability data obtained through storage up to 3 months at (b) (4) and (b) (4) (2 months for Lot 150241), and up to 12 months at (b) (4) for the development batch, indicate an increase in impurities over the course of stability for Relative Retention Times (RRT's) (b) (4) . Therefore, these impurities are in process of characterization and supporting data will be ready to provide in approximately 4-6 weeks from date of submission."*

The sixth specified impurity, (b) (4) is a known impurity (b) (4) (b) (4) is limited in the drug substance USP monograph to NMT (b) (4) %. The applicant has provided a justification for the proposed level for this impurity based on a literature search. (b) (4) (b) (4) is reported (b) (4)

Analytical procedures appear straightforward. Nimodipine Assay and Related Substances are determined using an isocratic reverse phase HPLC method [C18 column, water/methanol/THF mobile phase and detection by UV at 235 nm). A separate HPLC method is used for quantitation of methylparaben. The sponsor proposes a (b) (4) test; use of a specific test or addition of a second, orthogonal, nonspecific test will be recommended.

The NDA stability package is limited. In the initial submission, long-term (b) (4) and accelerated (b) (4) data through 3 months were provided for three pilot-scale batches of drug product packaged in the intended commercial configurations (16 ounce HDPE bottles and 20 mL HDPE cups). The pilot scale batches were manufactured at the proposed commercial facility. Additional stability data through 6 months were provided for two of the primary stability lots in the 10-Jan-2012 amendment. It is noted that the pilot scale batches were out of specification within 2 months under accelerated storage conditions and that testing at the intermediate storage condition (b) (4) was initiated at the 3 month time point. It is also noted that the first primary stability batch (Lot 0430) is reported to have failed release testing with individual impurities greater than (b) (4)%. The applicant's explanation for this is that the lot was tested 52 days after manufacture. Supportive data through 12 months long term and 6 months accelerated storage are provided for one research batch manufactured at the (b) (4) (b) (4) facility and packaged in 4 ounce HDPE bottles. The applicant proposes a (b) (4) month shelf life for product stored at room temperature.

Critical issues for review

Drug Substance

No critical issues related to the drug substance were identified during the initial assessment of the NDA or initial examination of the drug substance DMF.

Drug Product

A number of issues were identified during the initial assessment:

- *Impurities/Degradants*–-As discussed above, the applicant has not identified several specified degradation products observed in the drug product. Very limited information regarding LC-MS studies to characterize the impurities is provided in Module 3.2.P.8.1. Additionally, although the proposed limits for these impurities exceed the ICH qualification threshold applicant has not provided justification (e.g., nonclinical data or comparison with levels of these degradants in marketed products) for the proposed limits. This issue was discussed with the applicant in a teleconference held on 07-Dec-2011. At that time the applicant was advised that comparison to the impurity profiles of the marketed products might be a viable approach to impurity qualification. On 10-Jan-2012, the applicant submitted a CMC amendment providing the results of the comparison to approved capsule products from three sources (b) (4)). On initial examination of the amendment it does not appear that the data provided will be adequate to qualify the impurities. The sponsor has also proposed tightening the acceptance criteria for specified and total impurities; however, limits for three impurities would still exceed ICH qualification thresholds. The revised specification, however, is based on

HPLC-UV detection at (b) (4) nm, not (b) (4) nm as proposed in the original NDA submission. At the higher wavelength the percent peak area responses for the impurities are reduced relative to the response for the API. Since the impurities have not been identified there is no information available about relative response factors at either wavelength. Thus, there is no reason that UV quantitation at (b) (4) nm would be more appropriate than quantitation at (b) (4) nm.

- *Shelf Life*—Given the instability of the product, the limited stability data provided in the application, and the absence of information to support acceptance criteria greater than (b) (4)% for specified impurities, there does not appear to be sufficient data to establish any expiration dating for the product.

- *DMF Authorizations*—The sponsor references the following DMFs in the application:

  DMF (b) (4)) for Nimodipine
  DMF (b) (4) for HDPE (b) (4)
  DMFs (b) (4) and (b) (4) (held by various manufacturers) for (b) (4)
  the (b) (4) (i.e., (b) (4), etc.)

  Appropriate LoAs for DMFs (b) (4) and (b) (4) were included in the original application. For the remaining DMFs, however, the applicant submitted a letter from (b) (4) (the (b) (4)). No information was provided that would indicate that (b) (4) is authorized to act as an agent for any of the component manufacturers. This deficiency was corrected in the 10-Jan-2012 by submission of LoAs from the individual suppliers.

In addition to the issues discussed above, the following deficiencies were noted during the initial assessment:

- *Preservative Effectiveness*—The applicant proposes an acceptance criterion of (b) (4)%-(b) (4)% for (b) (4), methylparaben. No data to support the proposed limits could be located in the application.

- Given the instability of the product, the minimal stability data provided in the application, and the absence of any information to support acceptance criteria greater than (b) (4)% for the majority of the specified impurities, there does not appear to be sufficient data to establish any expiration dating period for the product.

- *Post-approval Stability Commitment*—The applicant commits to placing the first commercial batch on stability at (b) (4) and (b) (4) However, the second and third batch would only be placed on stability at (b) (4) The primary stability batches were manufactured at pilot scale; therefore, all three batches should be tested at (b) (4) Additionally the post-approval commitment does not include a provision for testing at (b) (4). Given the available stability information, the commitment should be revised.

- The following files freeze in Global Submit and Adobe Acrobat if text is selected. This appears to be an issue with the pdf files themselves, not a software issue. The applicant will be asked to correct this problem.

2.3.S	Manufacture
2.3.S	Characterization
2.3.S	Stability
3.2.S.3.2	Impurities
3.2.S.5	Reference Standards or Materials
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3	Stability Data

Additional issues

Administrative: The firm has submitted a claim for categorical exclusion under 21 CFR 25.31(b) which states that the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below one part per billion (1 ppb).

Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of nimodipine and nimodipine oral solution is provided in the submission. Facilities requiring compliance evaluation were submitted in EES on 13-Dec-2011.

Labeling/Established Name: The active ingredient, nimodipine, is not a salt. Therefore there are no issues of consistency between the established name "nimodipine oral solution" and the labeled potency.

Comments for RTF/74-Day Letter

With respect to (b) (4), methylparaben, you propose limits of (b) (4)%-(b) (4)% of label claim. Provide data to support the propose target level of methylparaben and the lower specification limit.

With respect to extractables and leachables, we note that you have submitted results of container extraction and migration studies. You should also monitor the primary stability batches for leachables through the proposed shelf life.

You propose a shelf life of (b) (4) months for product stored at room temperature. Given the instability of the product and the limited stability data provided in the application, there does not appear to be sufficient data to support the proposed shelf life.

With respect to the post-approval stability commitment, you propose to place the first commercial batch on stability at (b) (4). and (b) (4).; however, the second and third batch would only be placed on stability at (b) (4). All three of the first commercial batches should be tested under accelerated conditions. Additionally, the post approval stability protocol should incorporate storage at (b) (4). in case of significant change at (b) (4).

The following files freeze Global Submit and Adobe Acrobat if text is selected. This appears to be an issue with the pdf files themselves, not a software issue. We request that you correct this problem.

2.3.S	Manufacture
2.3.S	Characterization
2.3.S	Stability
3.2.S.3.2	Impurities
3.2.S.5	Reference Standards or Materials
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment
3.2.S.7.3	Stability Data

Review, Comments and Recommendation:

From a CMC perspective, the deficiencies noted above are considered review issues and the application is minimally fileable. Given the absence of any nonclinical data to qualify the drug product degradants, however, the question of fileability is deferred to the Pharm/Tox review team and the clinical division.

The drug substance is a well-characterized small molecule and the drug product is a simple oral solution. There are no QbD aspects to the submission. It is recommended that the review team include a single CMC reviewer and a Biopharmaceutics reviewer. The drug substance is not a new molecular entity; therefore, a Division-level regulatory briefing is not indicated.

{See appended electronic signature page}

Martha R. Heimann, Ph.D.
CMC Lead, DNDQA-1, ONDQA

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief, DNDQA-1, ONDQA

ATTACHMENT 1

Manufacturing Establishments for Nimodipine Oral Solution

Manufacturing information is reproduced from the attachment to Form 356h.

Manufacturer of Nimodipine, USP

Name and address	Responsibilities	Contact Person	Establishment Registration Information
(b) (4)	Drug substance - Synthesis - Release testing - Packaging - Labeling - Stability testing		(b) (4)

Manufacturer of Nimodipine Oral Solution, USP

Name and address	Responsibilities	Contact Person	Establishment Registration Information
Importfab 50 Hymus Blvd. Pointe-Claire QC, Canada H9R 1C9	Drug product - In-process testing - manufacturing - Packaging (16 oz) - Labeling	Luca Cianfaglia Quality Control Director *Email:* luca.c@importfab.com *Phone:* 514-694-0721 x224 *Fax:* 514-694-0854	3000999767 -Last FDA Inspection: August 10-13, 2009 -next FDA Inspection November 28, 2011 Ready for Inspection
(b) (4)	Drug Product - Stability storage - Alternate testing facility to (b) (4)	(b) (4)	(b) (4)
	Drug Product - Raw material testing - Release testing - Stability testing		
	Repackager/packager (20 mL unit-dose cups) - Package/lidding - carton		

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number:	**Supplement Number and Type:**	**Established/Proper Name:**
203-340	N/A	Nimodipine Oral Solution
Applicant:	**Letter Date:**	**Stamp Date:**
Arbor Pharmaceuticals	18-Nov-2011	18-Nov-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	Sponsor was advised that 12 months of long-term stability data and 6 month of accelerated data should be provided. Three months of data provided in initial NDA. Extended to 6 months for two of three primary batches in 10-Jan-2012 amendment.

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	N/A		
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Additional contact information requested by Quality Project Manager

8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Additional contact information requested by Quality Project Manager
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		Additional contact information requested by Quality Project Manager
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESSMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion claimed.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF
15.	Does the section contain controls for the DS?	X		Cross-reference to DMF and current USP
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	No clinical or bioavailability studies were performed to support this application.
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Stability data are provided; however, the data are inadequate to support the proposed expiry.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		Methods validation package included in Quality Overall Summary but not in Module 3.2.R. Sponsor will be asked to update application to correct location.

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	N/A		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?		X	No DMF referenced for unit-dose cups and lids. Information provided in NDA for review.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	15-Jun-2011	
	III			06-Jun-2011	
	III			27-Dec-2011	
	III			22-Dec-2011	
	III			15-Dec-2011	
	III			20-Dec-2011	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**Is the product quality section of the application fileable?**			
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	N/A		Describe filing issues here or on additional sheets
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Refer to 74 Day Letter comments above.

{See appended electronic signature page}
Martha R. Heimann, Ph.D.
CMC Lead, DNDQA-1, ONDQA

{See appended electronic signature page}
Ramesh Sood, Ph.D.
Branch Chief, DNDQA-1, ONDQA

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

/s/

MARTHA R HEIMANN
01/13/2012

RAMESH K SOOD
01/17/2012