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RESEARCH**

APPLICATION NUMBER:

203340Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

PRODUCT (Generic Name):	Nimodipine
PRODUCT (Brand Name):	Nymalize
NDA:	203-340
DOSAGE ROUTE:	Oral
DOSAGE FORM:	Solution (30 mg / 10 ml)
INDICATION:	Subarachnoid hemorrhage (SAH)
NDA TYPE:	Original
SUBMISSION DATES:	11/18/2011
SPONSOR:	Arbor Pharmaceuticals
REVIEWER:	Xinning Yang, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCP DIVISION:	DCP I, HFD 860
OND DIVISION:	HFD 120

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BACKGROUND

Nimodipine is a calcium channel blocker. This application submitted via 505(b)(2) route seeks approval of Nymalize™ (nimodipine oral solution) for the treatment of Subarachnoid hemorrhage (SAH) in adults. An orphan-drug designation was granted for this indication on September 16, 2011. This submission relies on previous findings of safety and effectiveness for the reference listed drug Nimotop® (nimodipine capsule), which was approved in 1988 under NDA 18-869 filed by Bayer. The capsule formulation was 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. The recommended dosing regimen is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. However, now Nimotop® has been discontinued.

The intention to provide an oral solution dosage form of nimodipine is to facilitate the correct administration of nimodipine in patients who cannot swallow and thus require nasogastric administration. An oral solution form eliminates the need to extract the capsule contents with a syringe, as currently required, and thereby should reduce the incidence of accidental intravenous administration which can lead to severe adverse events including death. The availability of oral solution will also allow for more precise dosing of nimodipine in these patients. In addition, oral solution provides another option for patients who may not require nasogastric administration but have difficulty swallowing oral capsules. The proposed dosage and administration for oral solution (nimodipine 60mg/20 ml) is consistent with the approved dosage and administration for the oral capsule (Nimotop®).

There are no clinical studies in this submission. The sponsor requested waiver of evidence of *in vivo* bioavailability or bioequivalence for its oral solution product. Nimotop® capsules are formulated as liquid filled soft gelatin capsules. After oral administration, peak concentrations of nimodipine are generally attained within one hour. The sponsor considered that the indication, route of administration, and dosing regimen are consistent between its oral solution product and the approved oral capsules. In addition, the sponsor stated that the oral solution form contains similar excipients as the immediate-release oral capsule formulation. Biowaiver was granted by the Division. Please refer to Biopharmaceutical review documented by Dr. Kareen Riviere for details.

REVIEW

Drug product stability data show that several impurities have presented above the ICH identification and qualification thresholds for nimodipine oral solution. Among these, one impurity has been identified and designated as (b) (4), which is present in development stability of the drug product at (b) (4) under accelerated storage condition for 6 months. Please refer to the Chemistry review and Pharmacology & Toxicology review of this NDA for more details.

Based on the analyses by API manufacturer (b) (4) the identity of (b) (4) a (b) (4)

(b) (4)

In 1986, Ramsch et. al. published a study describing the human metabolism of three calcium channel blockers (Am J Nephrol. 1986;6 Suppl 1:73-80). Included in this paper was an evaluation of the PK of nimodipine tablets (3 x 20mg) in 6 healthy adult subjects and a description of the plasma concentration-time curves for parent nimodipine and three major metabolites (M-I, M-II and M-III); an HPLC procedure was used for these determinations. In addition, the main metabolic pathway for nimodipine was presented. As shown in the figure below, metabolite M-I

Figure 1. Main Metabolic Pathway of Nimodipine (From Ramsch, et al., Figure 10).

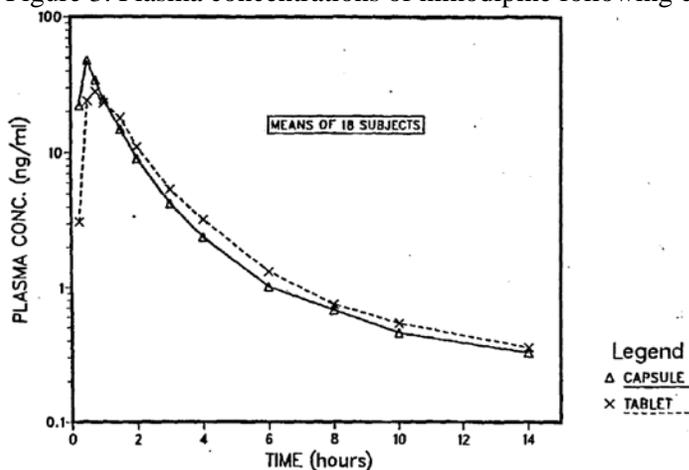
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As shown in the following figure, nimodipine mean plasma concentrations after a 60 mg oral dose are similar to those of metabolite M-I; they have similar peak exposures though the elimination half-life appears somewhat shorter for metabolite M-I.

Figure 2. Nimodipine (left panel) and its Metabolites (M-I, M-II, M-III, right panel) Mean Plasma Concentrations, n=6 healthy subjects given a single oral dose. (From Ramsch, et. al., Figure 6 and 11)

The PK profile of oral nimodipine depicted in Figure 2 is similar to that shown for clinical PK study D86-036-01 (n=18 subjects) for a single oral dose of 60 mg (tablet and capsule) as reported in the Summary Basis for Approval (SBA) for Nimotop[®] NDA 18-869 approved in 1988, though the C_{max} seem to be lower than that from study D86-036-01 (Figure 3).

Figure 3. Plasma concentrations of nimodipine following capsule and table doses of 60 mg.



The SBA also states that the major routes of nimodipine metabolism are demethylation of the ethoxymethoxy ether, dehydrogenation of the pyridine analogue, cleavage of the ester groups by hydrolysis to carboxylic acids, and hydroxylation of methyl group with subsequent glucuronide conjugation. Dehydrogenation of the pyridine analogue produces a metabolite BAY m8922 which has the same chemical structure as that of metabolite M-I ^{(b) (4)}.

The oral bioavailability of nimodipine is about 13% in humans. Thus, for a nimodipine dose of 60 mg, about 7.8 mg nimodipine enters systemic circulation. As shown above, the exposure of M-I formed *in vivo* is comparable or slightly lower than that of nimodipine.

The molecular weight of M-I is very close to nimodipine. Thus, it is assumed that such exposure of M-I corresponds to 7.8 mg or slightly lower dose of M-I, if pre-formed M-I is directly given to humans instead of nimodipine. Here, two assumptions are made. First, we assume that M-I has an oral bioavailability of 100%. If not, a dose of M-I more than 7.8 mg would be needed to achieve similar exposure of M-I to that obtained after administration of nimodipine. Secondly, systemic clearance for M-I is assumed to be the same as CL_{sys} of nimodipine. As shown in Figure 2, concentrations of M-I decreased more rapidly than parent drug, implying that M-I clearance might be higher than that of nimodipine. If that is the case, an amount of M-I dose higher than 7.8 mg would be needed to compensate faster clearance. Therefore, the number of 7.8 mg for M-I dose is a conservative estimation for the amount of pre-formed M-I needed to be given to reach similar exposure as observed after dosing of nimodipine.

(b) (4)

RECOMMENDATION

The risk of exposure to (b) (4) presented as degradation product in Nymalize™ (nimodipine) oral solution has been adequately characterized. There is no additional risk related to (b) (4). The potential risk associated with other impurities has been resolved by toxicology study in animals. Please refer to Pharmacology & Toxicology review of this NDA for details. In conclusion, this application is acceptable from a Clinical Pharmacology perspective.

Xinning Yang, Ph.D.
Division of Clinical Pharmacology I

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

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/s/

XINNING YANG
08/10/2012

YUXIN MEN
08/10/2012

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 203-340	Reviewer: Kareen Riviere, Ph.D.	
Submission Date:	November 18, 2011		
Division:	Neurology Products	Acting Biopharmaceutics Supervisory Lead: Angelica Dorantes, Ph.D.	
Applicant:	Arbor Pharmaceutics	Secondary Signature: Sandra Suarez-Sharp, Ph.D.	
Trade Name:	Nymalize	Date Assigned:	November 23, 2011
Generic Name:	Nimodipine oral solution	Date of Review:	April 24, 2012
Indication:	To improve neurological outcome in patients with subarachnoid hemorrhage (SAH) due to ruptured aneurysms	Type of Submission: 505(b)(2) New Drug Application	
Formulation/strengths:	Solution/ 60 mg per 20 mL		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(2) New Drug Application for 60 mg per 20 mL Nimodipine oral solution. The indication is for the improvement of neurological outcome in patients with subarachnoid hemorrhage (SAH) due to ruptured aneurysms.

Nimodipine is currently approved as Nimotop® capsules (NDA 18-869; approved in 1988) and as other generic capsules. Nimotop® capsules are formulated as liquid filled soft gelatin capsules for oral administration. The Applicant's intent is to market an oral solution dosage form of nimodipine to facilitate the administration of nimodipine in patients who cannot swallow and require nasogastric administration. The oral solution dosage form would eliminate the need to extract the capsule contents with a syringe, as currently required, and thereby may reduce the incidence of intravenous administration. The Applicant proposes that Nymalize be administered through a naso-gastric tube as well.

This submission includes a request to waive the in vivo bioavailability studies for the proposed product. To support the waiver request, the Applicant provided:

1. A qualitative description of the proposed product formulation and the formulation of the reference product,
2. Published literature containing pharmacokinetic data for an oral solution of nimodipine (60 mg dose), and
3. A comparison of the dosage and administration of the proposed product formulation versus the formulation of the reference product.

The Biopharmaceutics review for this NDA is focused on the acceptability of the waiver request.

The qualitative description of the proposed product formulation and the formulation of the reference product demonstrates that the proposed product and the Reference Product (Nimotop®) do not contain any inactive ingredients that may significantly alter the bioavailability of nimodipine.

The pharmacokinetic data from published literature suggest that the bioavailability of an oral solution of nimodipine is comparable to that of the Reference Product when its contents are administered as an oral solution.

The dosage and administration of the proposed product formulation versus the formulation of the Reference Product reveals that the proposed product will be administered similarly as the Reference Product in patients who cannot swallow and require nasogastric administration.

RECOMMENDATION:

This application is recommended for approval from a Biopharmaceutics standpoint. A waiver from the CFR requirement to conduct in vivo bioavailability studies is granted for the proposed product for the following reasons:

1. Since the label of the reference product allows for the capsule contents to be given as an oral solution, then similar dosage form can be implied. The oral solution contains nimodipine in a similar concentration as the reference product when given as an oral solution;
2. The composition of the proposed oral solution does not contain any known inactive ingredients that may alter the bioavailability of nimodipine;
3. The composition of the Reference Product does not contain any known inactive ingredients that may alter the bioavailability of nimodipine;
4. There is published pharmacokinetic data for nimodipine oral solution which indicates that nimodipine oral solution has comparable bioavailability to the Reference Product when its contents are administered as an oral solution; and
5. Based on current clinical practice described in the label of the Reference Product, the GI safety of the proposed oral solution is implied.

Kareen Riviere, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph.D.

Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

cc: Angelica Dorantes, Ph.D.

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

A. Formulation Comparison

The currently approved Nimotop® capsules are formulated as liquid filled soft gelatin capsules for oral administration. As stated in the label for Nimotop® capsules, each liquid filled capsule contains 30 mg of nimodipine in a vehicle of glycerin, peppermint oil, purified water and polyethylene glycol 400. The soft gelatin capsule shell is composed of gelatin, glycerin, purified water and titanium dioxide. The dosage and administration section of the label for Nimotop® capsules states that the oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days.

The structure of nimodipine is presented in Figure 1.

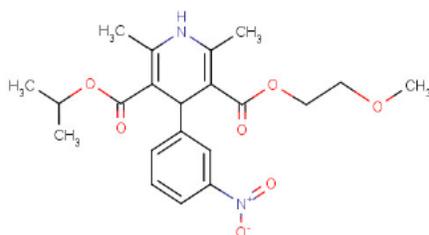


Figure 1. Chemical Structure of Nimodipine

The proposed product contains 60 mg of nimodipine per 20 ml. Table 1 highlights the composition of the proposed product. The proposed product contains some of the inactive ingredients that were present in the reference product, such as polyethylene glycol 400, purified water, and glycerin. None of the inactive ingredients present in the proposed product are known to alter the bioavailability or absorption of drugs. The proposed dosage and administration section in the proposed label for nimodipine oral solution states that the oral dose is 20 mL (60 mg) every 4 hours for 21 consecutive days.

Table 1. Quantitative Composition of 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	Active	USP			
Ethyl alcohol (b) (4)	(b) (4)	USP			
Methylparaben		NF			
Purified Water		USP			
Sodium Phosphate Monobasic Monohydrate		USP			
Sodium Phosphate Dibasic Dihydrate		USP			
Glycerin		USP			
Polyethylene Glycol 400		NF			

Reviewer's Comments and Evaluation:

The formulations of the proposed and reference products contain some similar ingredients. Since the reference product was approved in 1988, it is difficult to extract a record of its quantitative composition. Therefore, making a quantitative comparison of the proposed product and reference product is not feasible. Nonetheless, the formulations of the proposed product and the RLD do not contain any inactive ingredients that may significantly alter the bioavailability of nimodipine.

2. Nimodipine Pharmacokinetic Data

The label for Nimotop® capsules states that nimodipine is rapidly absorbed after oral administration and peak concentrations are generally attained within one hour. However, the bioavailability of nimodipine averages 13% after oral administration because of its high first-pass metabolism.

In this NDA, the Applicant references a published study conducted by Bayer AG that includes pharmacokinetic data for an I.V., tablet, and oral solution formulation of nimodipine (refer to Tables 2, 3, and 4). Note that Bayer is the sponsor for Nimotop® capsules.

Table 2. Mean Pharmacokinetic Parameters of Orally Administered Nifedipine (NF), Nitrendipine (NT), and Nimodipine (NM) as I.V. Bolus Injections (adapted from Ramsch et al. Am. J. Nephrol., 1986)

Drug	AUC _{0-∞} h·ng/ml	Cl ₁₀₁ ml/min/kg	V _{ss} l/kg	V _c l/kg	Elimination half-life, h	Dose mg/kg	Number of subjects
NF	65.4 ± 30.4	7.6 ± 4.0	0.47 ± 0.13	0.09 ± 0.08	2.5 ± 2.4	0.024	7
NT	25.2 ± 18.2	34.5 ± 16.6	6.6 ± 5.5	0.54 ± 0.51	4.6 ± 2.4	0.04	9
NM	38.8 ± 13.3	14.0 ± 4.0	0.94 ± 0.41	0.43 ± 0.33	1.1 ± 0.2	0.03	6

Table 3. Mean Pharmacokinetic Parameters of Orally Administered Nifedipine (NF), Nitrendipine (NT), and Nimodipine (NM) Solid Oral Preparations (adapted from Ramsch et al. Am. J. Nephrol., 1986)

Drug	Oral dose mg	C _{max} ng/ml	t _{max} h	AUC _{0-∞} h·ng/ml	Elimination half-life, h	F %	Number of subjects
NF capsule (10 mg)	2×10	146.6 ± 59.2	0.7 ± 0.3	386.7 ± 82.3	3.9 ± 2.3	40-60	6
NT tablet (20 mg)	20	9.4 ± 9.1	1.6 ± 1.0	29.5 ± 27.4	2.0 ± 0.8	10-30	20
NM tablet (20 mg)	3×20	20.6 ± 11.8	0.8 ± 0.3	42.0 ± 29.4	1.7 ± 1.1	5-10	6

C_{max} = Maximal plasma concentration; t_{max} = time of maximal plasma concentration; F = systemic bioavailability.

Table 4. Mean Pharmacokinetic Parameters of Orally Administered Nifedipine (NF), Nitrendipine (NT), and Nimodipine (NM) as Solution (adapted from Ramsch et al. Am. J. Nephrol., 1986)

Drug	Oral dose mg	C _{max} ng/ml	t _{max} h	AUC _{0-∞} h·ng/ml	Elimination half-life, h	Number of subjects
NF	10	56.0 ± 23.0	0.46 ± 0.19	134.3 ± 58.3	4.6 ± 2.5	6
NT	20	50.3 ± 43.0	0.52 ± 0.11	59.8 ± 63.9	1.2 ± 2.1	18
NM	60	116.5 ± 74.3	0.33 ± 0.12	107.6 ± 51.4	1.70 ± 0.89	6

C_{max} = Maximal plasma concentration; t_{max} = time of maximal plasma concentration.

Ramsch et al. state that a commercial tablet preparation of Nimotop® has a bioavailability of 5-10% after administering a 20 mg dose (refer to Table 3). However, Ramsch et al. did not calculate the bioavailability of the

nimodipine oral solution, which was prepared in a mixture of water plus organic solvent (polyethylene glycol, ethanol, or cremaphor).

Reviewer’s Comments and Evaluation:

This reviewer calculated the bioavailability of the nimodipine oral solution based on the above published PK data for the I.V. formulation (Table 2) and oral solution (Table 4) using the following equation:

$$F = \frac{AUC_{po} \times Dose_{IV}}{AUC_{IV} \times Dose_{po}}$$

The calculated bioavailability of nimodipine oral solution used in the study by Ramsch et al. for different body weights is shown in Reviewer’s Table 1.

Reviewer’s Table 1. Calculated Bioavailability of Nimodipine Oral Solution (60 mg dose)
Using PK Data from Ramsch et al. Am. J. Nephrol., 1986

Body Weight (kg)	Bioavailability (F, %)
70	9.7
80	11.1
90	12.5
100	13.9
120	16.7

The nimodipine oral solution used in this published study has a bioavailability of approximately 10-17% (based on body weight of 70 - 120 kg) after administering a 60 mg dose. The bioavailability of the Nimotop® capsules (13%) stated in the label for the reference product is within this range. The bioavailability of the proposed oral solution is expected to be similar to that of the oral solution used in this published literature because neither formulation contains any known inactive ingredients that may alter the bioavailability of nimodipine.

Therefore, the data above suggest that the bioavailability of the proposed product is expected to be similar to that of the Reference Product when its contents are administered as an oral solution.

3. Comparison of the Dosage and Administration

The label for Nimotop® capsules includes the following instructions for patients with a nasogastric or gastric tube in place:

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. A parenteral syringe can be used to extract the liquid inside the capsule, but the liquid should always be transferred to a syringe that cannot accept a needle and that is designed for administration orally or via a nasogastric tube or PEG. To help minimize administration errors, it is recommended that the syringe used for administration be labeled “Not for IV Use”. The contents should then be emptied into the patient’s in situ nasogastric tube and washed down the tube with 30 mL of normal saline (0.9%). The efficacy and safety of this method of administration has not been demonstrated in clinical trials.

In the dosage and administration section of the proposed label for nimodipine oral solution, the Applicant has also included instructions for patients with a nasogastric or gastric tube in place:



Reviewer's Comments and Evaluation:

Nimotop®'s label allows for the contents of the capsules to be extracted and then administered as a solution (~1.5 mg/mL) via a nasogastric tube. The proposed label for nimodipine oral solution is consistent with the currently approved dosage and administration for Nimotop® capsules except for sections specific for removal of the capsule contents for nasogastric tube administration. Additionally, the proposed label allows for a ~1.5 mg/mL nimodipine solution to be given to patients with a nasogastric or gastric tube in place. Thus, it can be concluded that the dosage form of the proposed product will be similar to that of the reference product when administered to patients with a nasogastric or gastric tube in place.

Reviewer's Overall Assessment:

According to the 21 CFR 320.22(b)(3), a biowaiver may be granted for an oral solution if the following requirements are met:

- 1. The oral solution contains an active ingredient in the same concentration and dosage form as the reference product; and*
- 2. The composition of the oral solution does not contain any inactive ingredients that may significantly alter the bioavailability of the active ingredient.*

A waiver from the CFR requirement to conduct in vivo bioavailability studies is granted for the proposed product for the following reasons:

- 1. Since the label of the reference product allows for the capsule contents to be given as an oral solution, then similar dosage form can be implied. The oral solution contains nimodipine in a similar concentration as the reference product when given as an oral solution;*
- 2. The composition of the oral solution does not contain any known inactive ingredients that may alter the bioavailability of nimodipine; also*
- 3. The composition of the Reference Product does not contain any known inactive ingredients that may alter the bioavailability of nimodipine;*
- 4. There is published pharmacokinetic data for nimodipine oral solution that indicates that nimodipine oral solution has comparable bioavailability to the Reference Product when its contents are administered as an oral solution; and*
- 5. Based on current clinical practice described in the label of the Reference Product, the GI safety of the proposed oral solution is implied.*

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/s/

KAREEN RIVIERE
04/24/2012

SANDRA SUAREZ
04/24/2012

*Office of Clinical Pharmacology
New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA Number	N 203340	Brand Name	Nymalize™
OCP Division (I, II, III)	DCP-I	Generic Name	Nimodipine
Medical Division	HFD-120	Drug Class	Calcium Channel Blocker
OCP Reviewer	Xinning Yang	Indication(s)	Subarachnoid hemorrhage in Adults
OCPB Team Leader	Angela Men	Dosage Form	Oral Solution (60 mg / 20 mL)
		Dosing Regimen	20 mL (60 mg) every 4 hours for 21 consecutive days
Date of Submission	11/18/2011	Route of Administration	Oral
Estimated Due Date of OCP Review	03/18/2012	Sponsor	Arbor Pharmaceuticals
Division Due Date	05/03/2012	Priority Classification	Priority (Orphan drug)
PDUFA Due Date	05/18/2012		

Clin. Pharm. and Biopharm. Information

This application for Nymalize™ (Nimodipine oral solution) is being submitted via 505(b)(2) route under NDA 203-340 for the treatment of Subarachnoid hemorrhage (SAH) in adults. An orphan-drug designation was granted for this indication on September 16, 2011. This submission relies on previous findings of safety and effectiveness for the listed drug Nimotop® (nimodipine capsule) via cross reference to NDA 18-869 sponsored by Bayer Healthcare, which has been discontinued.

Nimodipine is a calcium channel blocker. The capsule formulation is currently indicated 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. The recommended dosing regimen is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days.

The intention to provide an oral solution dosage form of nimodipine is to facilitate the correct administration of nimodipine in patients who cannot swallow and thus require nasogastric administration. An oral solution form eliminates the need to extract the capsule contents with a syringe, as currently required, and thereby should reduce the incidence of accidental intravenous administration which can lead to severe adverse events including death. The availability of oral solution will also allow for more precise dosing of nimodipine in these patients. In addition, oral solution provides another option for patients who may not require nasogastric administration but have difficulty swallowing oral capsules. The proposed dosage and administration for Oral Solution (nimodipine 60mg/ 20 ml) is consistent with the currently approved dosage and administration for Oral Capsule 30 mg.

There are no clinical studies in this submission. The sponsor requested waiver of evidence of in vivo bioavailability or bioequivalence for its oral solution product. Nimotop® capsules are formulated as liquid filled soft gelatin capsules. After oral administration, peak concentrations of nimodipine are generally attained within one hour. The sponsor considered that the indication, route of administration, and dosing regimen are consistent between its oral solution product and the approved oral capsules. In addition, the sponsor stated that the oral solution form contains similar excipients as the immediate-release oral capsule formulation.

Filability and QBR comments		
	“X” if yes	Comments
Application filable?	X	
Comments sent to firm?		
QBR questions (key issues to be considered)	No Clinical studies conducted. The submission only contains quality information/data.	
Other comments or information not included above		
Primary reviewer Signature and Date	Xinning Yang	
Secondary reviewer Signature and Date	Angela Men	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

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

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

Xinning Yang	12/06/2011
Reviewing Clinical Pharmacologist	Date
Angela Y. Men	12/06/2011
Team Leader/Supervisor	Date

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/s/

XINNING YANG
02/01/2012

YUXIN MEN
02/14/2012

BIOPHARMACEUTICS FILING REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 203-340	Reviewer: Kareen Riviere, Ph.D.	
Submission Date:	November 18, 2011		
Division:	DNP	Biopharmaceutics Lead: Angelica Dorantes, Ph.D.	
Sponsor:	Arbor Pharmaceutics	Secondary Signature: Sandra Suarez-Sharp, Ph.D.	
Trade Name:	Nymalize	Date Assigned:	November 23, 2011
Generic Name:	Nimodipine oral solution	Date of Review:	January 19, 2012
Indication:	To improve neurological outcome in patients with subarachnoid hemorrhage (SAH) due to ruptured aneurysms	Type of Submission: 505(b)(2) New Drug Application	
Formulation/strengths:	Solution/ 60 mg per 20 mL		
Route of Administration:	Oral		

SUMMARY OF BIOPHARMACEUTICS FINDINGS

This is a 505(b)(2) New Drug Application for 60 mg per 20 mL Nimodipine oral solution. The indication is for the improvement of neurological outcome in patients with subarachnoid hemorrhage (SAH) due to ruptured aneurysms.

BIOPHARMACEUTIC INFORMATION:

Nimodipine is currently approved as Nimotop® capsules (NDA 18-869) and other generic capsules. Nimotop® capsules are formulated as liquid filled soft gelatin capsules for oral administration.

The Applicant's intention is to provide an oral solution dosage form of nimodipine to facilitate the correct administration of nimodipine in patients who cannot swallow and require nasogastric administration. The oral solution dosage form would eliminate the need to extract the capsule contents with a syringe, as currently required, and thereby may reduce the incidence of IV administration. The Applicant also proposes that Nymalize be administered through a naso-gastric tube.

This submission includes a BA/BE waiver request for the proposed product. In general, granting a biowaiver for an oral solution drug product that is currently approved as a capsule drug product is not feasible from a regulatory perspective because the bioavailability of the drug substance in an oral solution may be higher than that in a capsule formulation. However, in this case, a BA/BE waiver may be granted for the proposed product because of the following reasons:

1. The oral solution contains nimodipine in the same concentration as the reference product;
2. The composition of the oral solution does not contain any known inactive ingredients that may alter the BA of the nimodipine; and
3. Based on current clinical practice described in the label of the reference drug product, the safety of the capsule contents given as an oral solution is well understood.

The acceptability of the waiver request will be a review issue and will be the focus of the Biopharmaceutics review.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 203-340 for filing purposes. We found this NDA **filable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission. There are no comments to the Applicant at this time.

Kareen Riviere, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Sandra Suarez-Sharp, Ph.D.

Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

cc: Angelica Dorantes, Ph.D.

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KAREEN RIVIERE
01/19/2012

SANDRA SUAREZ
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