CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076740

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-740
Drug Product Name	Nimodipine Capsules
Strength	30 mg
Applicant Name	Pliva, Inc.
Address	East Hanover, NJ
Submission Date(s)	May 14, 2004
Amendment Date(s)	December 10, 2004
Reviewer	**Hoainhon Nguyen**
First Generic	**Yes**
File Location	**V:\firmsnz\pliva\ltrs&rev\76740n0504.doc**

I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study and a single-dose, 2-way crossover nonfasting bioequivalence study comparing the test product, Nimodipine Capsules, 30 mg, with the RLD product, Bayer's Nimotop® (nimodipine) Capsules, 30 mg. The fasting study was performed in 16 normal males and 32 normal females at a dose of 1x30 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (AUCt 1.01, 95.2-108.0; AUCinf 1.01, 95.3-108.1; Cmax 0.98, 87.7-108.7). The nonfasting study was performed in 33 normal males and 12 normal females at a dose of 1x30 mg and resulted in acceptable data (point-estimate) that demonstrate BE in the fed state (AUCt 1.07; AUCinf 1.06; Cmax 1.12). The nonfasting study was conducted prior to the issuance of the Food Effect Study Guidance.

The firm has also submitted comparative dissolution profile for the test and reference products. The dissolution testing using the firm's proposed method has been found acceptable. However, the DBE recommends a different specification for the test product based on the data submitted: NLT (b) (4) (Q) in 30 minutes. Both the test and reference met the FDA-recommended specification at S1 level.

The firm is requested to acknowledge the FDA-recommended specification.

This application is **incomplete** pending the firm's response concerning the dissolution specification recommendation.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Nimodipine Capsules
Reference Product	Nimotop® Capsules, 30 mg
RLD Manufacturer	Bayer Corp.
NDA No.	18-869
RLD Approval Date	12/28/88
Indication	Indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage from ruptured congenital aneurysms who are in good neurological condition post-ictus (e.g., Hung and Hess Grades I-III).

B. PK/PD Information (Ref: PDR 2004)

Bioavailability	13%
Food Effect	In a study of 24 healthy male volunteers, administration of nimodipine capsules following a standard breakfast resulted in a 68% lower peak plasma concentration and 38% lower bioavailability relative to dosing under fasted conditions.
Tmax	1 hour
Metabolism/Excretion	Nimodipine is eliminated almost exclusively in the form of metabolites and less than 1% is recovered in the urine as unchanged drug. Numerous metabolites, all of which are either inactive or considerably less active than the parent compound, have been identified.
Half-life	1-2 hours
Relevant OGD or DBE History	**Control Document No. 00-119 ((b) (4); 03/05/00):** The DBE recommended a fasting bioequivalence study and a nonfasting bioequivalence study for the drug product. **Control Document No. 02-580 ((b) (4); 10/07/02):** The DBE recommended the same *in vivo* bioequivalence requirements as above. The firm was also informed that there was currently no dissolution method available and the firm should develop its own method for the drug product.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1(Telephone Amendment dated 12/10/04)

D. Pre-Study Bioanalytical Method Validation

Analyte name	Nimodipine
Internal Standard	(b) (4)
Method description	LC/MS/MS
QC range	0.240, 3.00, 60.0 ng/mL
Standard curve range	0.0800-80.00 ng/mL
Limit of quantitation	0.0800 ng/mL
Average recovery of Drug (%)	98%
Average Recovery of Int. Std (%)	96%
QC Intraday precision range (%)	2.0-2.2%
QC Intraday accuracy range (%)	94.2-101.3%
QC Interday precision range (%)	3.9-5.8%
QC Interday accuracy range (%)	99.6-103.7%
Bench-top stability (hrs)	24 hours
Stock stability (days)	Not provided
Processed stability (hrs)	142 hours
Freeze-thaw stability (cycles)	6 cycles
Long-term storage stability (days)	16 weeks
Dilution integrity	Not provided
Specificity	Acceptable
SOPs submitted	No
Bioanalytical method is acceptable	Yes
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chrom	Serial

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	AA01369
Study Design	Two-way crossover
No. of subjects enrolled	48 plus 4 alternates
No. of subjects completing	52
No. of subjects analyzed	48 per protocol
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 16 Female: 32
Test product	Nimodipine Capsules, 30 mg
Reference product	Bayer's Nimotop® Capsules
Strength tested	30 mg
Dose	1x30 mg

Summary of Statistical Analysis, Fasting Bioequivalence Study (N=48)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.01	95.2-108.0
AUC_{∞}	1.01	95.3-108.1
C_{max}	0.98	87.7-108.7

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Non-analytical Repeats	2	5	0.1	0.3	2	1	0.1	0.06

Did use of recalculated plasma concentration data change study outcome? No

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	AA01414
Study Design	Two-way crossover
No. of subjects enrolled	50
No. of subjects completing	45
No. of subjects analyzed	45
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 33 Female 12
Test product	Nimodipine Capsules, 30 mg
Reference product	Bayer's Nimotop® Capsules
Strength tested	30 mg
Dose	1x30 mg

Summary of Statistical Analysis, Fed Bioequivalence Study (N=45)		
Parameter	Point Estimate	90% Confidence Interval
AUC_{0-t}	1.07	102.3-111.8
AUC_{∞}	1.06	101.8-111.2
C_{max}	1.12	97.7-127.6

Reanalysis of Study Samples, Fed Bioequivalence Study Additional information in Appendix, Table 17								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
There was no PK repeat sample.								

F. Formulation

Location in appendix	SectionIV.B, Page 25
Are inactive ingredients within IIG limits?	No
If no, list ingredients outside of limits	PEG (b) (4). See Comments under IV. Appendix B. Formulation
If a tablet, is the product scored?	N/A
If yes, which strengths are scored?	
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	

G. In Vitro Dissolution

Source of Method	Firm*
Medium	0.5% Sodium Docedyl Sulfate
Volume (mL)	900
USP Apparatus type	II (paddle)
Rotation (rpm)	50
Firm's proposed specification	NLT (b) (4) (Q) in 30 minutes
FDA's specification based on data submitted	NLT (Q) in 30 minutes
F2 metric calculated?	No
If no, reason why F2 not calculated	Both products are fast dissolving.
Is method acceptable?	Yes.
If not then why?	

***NOTE:** Currently, there is no USP or FDA dissolution method.

H. Waiver Request(s)

Strengths for which waivers are requested	None
Regulation cited	
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A

I. Deficiency Comments

Currently, there is no FDA or USP dissolution method. The firm's proposed method has been found acceptable. However, the DBE recommends a different specification for the test product based on the data submitted: NLT (b) (4) (Q) in 30 minutes. Both the test and reference met the FDA-recommended specification at S1 level. (NOTE: Dr. S. Nerurkar discussed the FDA-recommended specification with DBE's Dissolution specialist, Dr. N. Tran, and Dr. Tran concurred.)

We request that the firm acknowledge the FDA-recommended specification.

J. Recommendations

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by Pliva on the test product, Nimodipine Capsules, 30 mg, lot # XPP0204004, comparing it with the reference product, Bayer's Nimotop® (nimodipine) Capsules, 30 mg, lot # 25P0039, have been found **acceptable** by the Division of Bioequivalence. The test product, Pliva's Nimodipine Capsules, 30 mg, is bioequivalent to the reference product, Bayer's Nimotop® (nimodipine) Capsules, 30 mg, under fasting and nonfasting conditions.

2. The dissolution testing conducted by Pliva on its Nimodipine Capsules, 30 mg, is **acceptable**.

The dissolution testing should be conducted in 900 mL of water with 0.5% SDS at 37°C using USP apparatus II(paddle) at 50 rpm. The test product should meet the following specification:

Not less than (b) (4) (Q) of the labeled amounts of the drug in the dosage form is dissolved in 30 minutes.

The FDA-recommended specification is different from the firm's proposed specification. **We request that the firm acknowledge the FDA-recommended specification.**

2/8/05

Hoainhon Nguyen, Team I, Date Signed

2/8/2005

Shriniwas Nerurkar, Team I, Date Signed

2/8/05

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	AA01369
Study Title	Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailablity Study of Sidmak and Bayer (Nimotop®) 30 mg Nimodipine Capsules in Healthy Volunteers Under Fasting Conditions
Clinical Site	MDS Pharma Services, Quebec, Canada
Principal Investigator	Gaetano Morelli, M.D.
Study/Dosing Dates	09/19/02-09/28/02
Analytical Site	MDS Pharma Services, Lincoln, NE
Analytical Director	(b) (6) Ph.D.
Analysis Dates	10/03/02-10/27/02
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	38 days

Treatment ID	**Test**	**Reference**
Product Name	Nimodipine	Nimotop®
Manufacturer	Pliva	Bayer
Batch/Lot No.	XPP0204004	25P0039
Manufacture Date	05/02	
Expiration Date		07/03
Strength	30 mg	30 mg
Dosage Form	Capsules	Capsules
Batch Size	(b) (4)	
Production Batch Size		
Potency	99.1%	99.6%
Content Uniformity (mean, %CV)	98.1%(RSD=0.8%)	98.6%(RSD=1.9%)
Formulation	See Appendix Section B	
Dose Administered	1x30 mg	1x30 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	Yes
Blood Sampling Times	Predose, 0.167, 0.25, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours postdose.
Blood Volume Collected/Sample	10 mL/sample
Blood Sample Processing/Storage	Blood samples were collected in Vacutainers® collection tubes containing EDTA, centrifuged and harvested for plasma which was stored at -20°c until analysis. Due to the sensitivity of nimodipine to light, the sample collection and processing were done under conditions which minimized the light exposure.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Approximately 10 hours prior to dosing until 4 hours postdose
Length of Confinement	Approximately 10 hours prior to dosing until 24 hours postdose
Safety Monitoring	Vital signs (seated blood pressure and heart rate) were taken at predose and at 1, 2, 4 and 6 hours postdose. Subjects were monitored for adverse effects during the study periods.

Comments on Study Design: Acceptable

b) Clinical Results

Table 1 Demographics of Study Subjects (N=48)

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	95.8
Mean	36.60	Mean	70.94	18-40	60.4	Male	66.7	Afr. Amer.	4.2
SD	9.30	SD	8.61	41-64	39.6	Female	33.3	Hispanic	0.0
Range	20	Range	52.4	65-75	0.0			Asian	0.0
	53		94	>75	0.0			Others	0.0

Table 2 Dropout Information

There was no dropout. Four alternates were not used in the study.

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Headache	11	17
Runny nose		2
Nausea	3	4
Vomited	3	
Pain in right leg	1	
Pain in left leg	1	
Blocked nose		1
Pain in right arm		1
Pain venipuncture site		1
Wretching		1
Dizziness	3	3
Neck pain		1
Abdominal cramps	1	1
Pain in sinus		1
Left neck pain		1
Pain left venipuncture site	1	
Feels hot	2	
Trembling		1
Throat discomfort		1
Coughing		1
Feels cold		1
Fever		1
Chest spasms		1
Bruise at catheter site		1
Itching all over body		1
Total	26	42

Table 4 Protocol Deviations

There was no significant protocol deviation that might have compromised the integrity of the study. Deviations in blood sampling were corrected by using the actual sampling times if the deviation was greater than 5% (in the reviewer's analysis).

Comments on Dropouts/Adverse Events/Protocol Deviations: None

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

	Nimodipine			
QC Conc. (ng/mL)	0.240 (n=48)	3.00 (n=48)	60.00 (n=48)	60.00 dil.x2(n=2)
Inter day Precision (%CV)	8.19	2.79	5.41	NA
Inter day Accuracy (%)	96.67	101.7	102.9	109.2
Cal. Standards Conc. (ng/mL)	0.080, 0.200, 0.500, 2.00, 5.00, 20.00, 50.00, 70.00, 80.00			
Inter day Precision (%CV)	2.00-5.56			
Inter day Accuracy (%)	98.64-101.9			
Linearity Range (range of R^2 values)	0.9987-0.9998			

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected.

Comments on Chromatograms: Acceptable

Table 6 SOP's dealing with analytical repeats of study samples

The SOP No. GL-BI-10603-01 ("Reporting of Data Generated from the Analysis of Biological Matrices") was submitted in the Telephone Amendment dated 12/10/04 per the DBE's request. However, the SOP was effective only after the analysis of the samples was already initiated (Effective date of the SOP was 10/15/02; the analysis was between 10/03/02-10/27/03.)

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes. See comments concerning the effective date of the SOP above.
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	The reviewer recalculated the study results using all original values. The study outcome remained the same as that determined by the firm.
If no, reason for disagreement	

Summary/Conclusions, Study Assays: The analytical method validation is acceptable.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=48)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	Ng.hr/mL	47.31	55	45.77	49	1.03
AUC∞	Ng.hr/mL	48.84	55	47.22	49	1.03
Cmax	Ng/mL	32.67	60	32.83	50	1.00
Tmax	Hrs	0.74	41	0.70	86	1.06
T1/2	Hrs	6.64	40	6.43	39	1.03
Kel	Hr^{-1}	0.126	62	0.130	61	0.97

Table 9 Geometric Means and 90% Confidence Intervals (N=48)

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC0-t	41.31	40.74	1.01	95.2-108.0
AUC∞	42.68	42.06	1.01	95.3-108.1
Cmax	27.45	28.12	0.98	87.7-108.7

Table 10 Additional Study Information

Root mean square error, AUC0-t	0.185151
Root mean square error, AUC∞	0.183549
Root mean square error, Cmax	0.313816
Kel and AUC∞ determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes except for one subject (#37, Period I, Test Treatment). However, the study outcome based on both the reviewer and firm was the same.
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as Cmax	0
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: None

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The fasting study is acceptable. The 90% confidence intervals for lnCmax, lnAUCt and lnAUCinfinity were within the acceptable limits of [80.0-125.0].

Table 11 Nimodipine Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (ng/mL)

Test Treatment

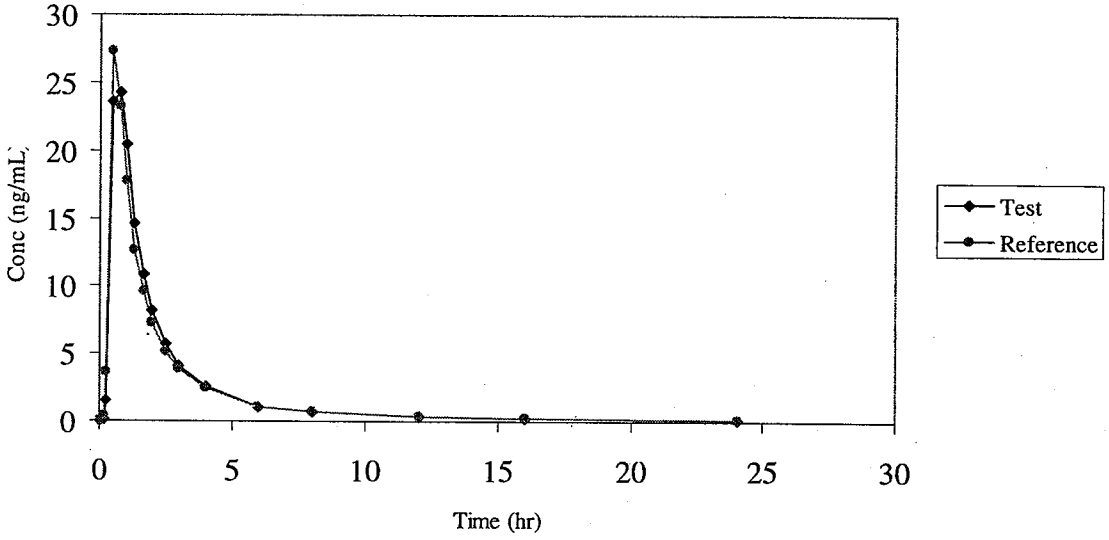
Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	48	0.000	0.000	0.000	0.000
Hour0.167	48	0.060	0.296	0.000	1.680
Hour0.25	48	1.537	4.365	0.000	23.530
Hour0.50	48	23.619	21.469	0.000	105.170
Hour0.75	48	24.228	13.440	1.870	63.480
Hour1	48	20.454	14.107	2.650	85.000
Hour1.333	48	14.595	9.876	3.560	53.730
Hour1.667	48	10.830	7.016	2.440	36.340
Hour2	48	8.207	4.870	2.020	26.340
Hour2.50	48	5.700	3.195	1.360	15.100
Hour3	48	4.070	2.123	1.180	9.620
Hour4	48	2.521	1.594	0.690	9.590
Hour6	48	1.026	0.657	0.000	3.050
Hour8	48	0.739	0.508	0.200	3.000
Hour12	48	0.381	0.292	0.000	1.590
Hour16	48	0.254	0.209	0.000	1.030
Hour24	48	0.116	0.112	0.000	0.590

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	48	0.000	0.000	0.000	0.000
Hour0.167	48	0.324	1.128	0.000	5.380
Hour0.25	48	3.649	7.585	0.000	32.560
Hour0.50	48	27.348	18.710	0.210	64.800
Hour0.75	48	23.232	14.645	1.900	68.130
Hour1	48	17.770	10.913	3.480	56.510
Hour1.333	48	12.636	7.415	3.560	39.390
Hour1.667	48	9.611	6.393	2.880	37.000
Hour2	48	7.259	4.303	2.300	24.220
Hour2.50	48	5.155	2.765	1.630	13.670
Hour3	48	3.862	2.068	1.320	10.680
Hour4	48	2.491	1.596	0.770	10.350
Hour6	48	1.073	0.559	0.260	2.720
Hour8	48	0.745	0.411	0.080	1.770
Hour12	48	0.367	0.221	0.000	0.880
Hour16	48	0.261	0.173	0.000	0.730
Hour24	48	0.107	0.095	0.000	0.340

Figure 1

Nimodipine Mean Plasma Concentrations
Fasting Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	AA01414
Study Title	Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailablity Study of Sidmak and Bayer (Nimotop®) 30 mg Nimodipine Capsules in Healthy Volunteers Under Fed Conditions
Clinical Site	MDS Pharma Services, Quebec, Canada
Principal Investigator	Gaetano Morelli, M.D.
Study/Dosing Dates	10/26/02-11/04/02
Analytical Site	MDS Pharma Services, Lincoln, NE
Analytical Director	(b) (6) Ph.D.
Analysis Dates	11/13/02-11/31/02
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	36 days

Treatment ID	**Test Product**	**Reference Product**
Product Name	Nimodipine	Nimotop®
Manufacturer	Pliva	Bayer
Batch/Lot No.	XPP0204004	25P0039
Manufacture Date	05/02	
Expiration Date		07/03
Strength	30 mg	30 mg
Dosage Form	Capsules	Capsules
Batch Size	(b) (4)	
Production Batch Size		
Potency	99.1%	99.6%
Content Uniformity	98.1%(RSD=0.8%)	98.6%(RSD=1.9%)
Formulation	See Appendix Section B	
Dose Administered	1x30 mg	1x30 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	Yes
Blood Sampling Times	Predose, 0.167, 0.25, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours postdose.
Blood Volume Collected/Sample	10 mL/sample
Blood Sample Processing/Storage	Blood samples were collected in Vacutainers® collection tubes containing EDTA, centrifuged and harvested for plasma which was stored at -20°c until analysis. Due to the sensitivity of nimodipine to light, the sample collection and processing were done under conditions which minimized the light exposure.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Length of Fasting before Meal	A standard breakfast was given 30 minutes following an approximately 10 hours overnight fast. The subjects fasted for a period of 4 hours postdose.
Length of Confinement	Approximately 10 hours predose until 24 hours postdose.
Safety Monitoring	Vital signs (seated blood pressure and heart rate) were taken at predose and at 1, 2, 4 and 6 hours postdose. Subjects were monitored for adverse effects during the study periods.
Standard FDA Meal Used?	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 rasher of Canadian bacon, 1 serving of hash brown potatoes, 180 mL of orange juice and 240 mL of whole milk.
If no, then meal is listed in table below	

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 12 Demographics of Study Subjects (N=45)

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0			Caucasian	75.6
Mean	35.07	Mean	70.47	18-40	66.7	Male	73.3	Afr. Amer.	15.6
SD	9.64	SD	7.32	41-64	33.3	Female	26.7	Hispanic	8.9
Range	18	Range	54.6	65-75	0.0			Asian	0.0
	55		84.6	>75	0.0			Others	0.0

Table 13 Dropout Information

Subject No	Reason	Period	Replaced?
6	Subject did not return for Period II for personal reasons	II	No
9	Subject did not return for Period II	II	No
13	Withdrawn prior to Period II due to possession of cannabis at time of check-in	II	No
49	Removed from the study prior to Period II due to adverse events	II	No
50	Left during Period I for personal reasons	I	No

NOTE: There were no Subjects #25 or 52.

Table 14 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
Feeling of thick tongue	1	
Itchiness	1	
Menstrual cramps	1	
Headache	8	8
Bruise at catheter site	2	
Upset stomach	1	
Sore throat		1
Redness at catheter site		1
Palpitations	1	
Thirsty	1	
Lack of concentration	1	
Nausea	1	
Dizziness	1	
Loose stool	1	
Nervous	1	
Tired	1	
Total	22	10

Table 15 Protocol Deviations

There was no significant protocol deviation that might have compromised the integrity of the study. Blood sampling deviations were corrected by using the actual sampling times if the deviation was greater than 5% (in the reviewer analysis).

Comments on Adverse Events/Protocol Deviations: None

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

	Nimodipine			
QC Conc. (ng/mL)	0.240 (n=30)	3.00 (n=31)	60.00 (n=32)	60.00 dil.x5(n=2)
Inter day Precision (%CV)	6.33	4.03	4.3	NA
Inter day Accuracy (%)	101.3	104.1	103.7	104.0
Cal. Standards Conc. (ng/mL)	0.080, 0.200, 0.500, 2.00, 5.00, 20.00, 50.00, 70.00, 80.00			
Inter day Precision (%CV)	2.48-6.47			
Inter day Accuracy (%)	97.40-102.1			
Linearity Range (range of R^2 values)	0.9957-0.9998			

Comments on Study Assay Quality Control: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected.

Comments on Chromatograms: The chromatograms were acceptable.

Table 17 SOP's dealing with analytical repeats

SOP No. GL-BI-10603-01, effective 10/15/2002, "Reporting of Data Generated from the Analysis of Biological Matrices"

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes.
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	The reviewer recalculated the study results using all original values. The study outcome remained the same as that determined by the firm.
If no, reason for disagreement	

Summary/Conclusions, Study Assays: The analytical method validation is acceptable.

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters (N=45)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	Ng.hr/mL	41.91	44	38.86	42	1.08
AUC_{∞}	Ng.hr/mL	43.49	44	40.59	42	1.07
C_{max}	Ng/mL	17.11	60	15.58	60	1.10
T_{max}	Hrs	1.69	41	1.60	52	1.06
$T_{1/2}$	Hrs	6.36	23	6.64	33	0.96
K_{el}	Hr^{-1}	0.116	27	0.117	37	0.99

Table 20 Geometric Means and 90% Confidence Intervals (N=45)

Parameter	Test	Reference	T/R	90% CI
	Mean	Mean		
AUC_{0-t}	38.42	35.92	1.07	102.3-111.8
AUC_{∞}	39.93	37.52	1.06	101.8-111.2
C_{max}	14.88	13.33	1.12	97.7-127.6

Table 21 Additional Study Information

Root mean square error, AUC_{0-t}	0.125357
Root mean square error, AUC_{∞}	0.123916
Root mean square error, C_{max}	0.376899
K_{el} and AUC_{∞} determined for how many subjects?	All
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	0
-first measurable drug concentration as C_{max}	0
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: None

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: The nonfasting study is acceptable. The 90% confidence intervals for lnAUCt and lnAUCinfinity were within the acceptable limits of [80.0-125.0]. The point estimate of lnCmax was within [0.80;1.25]. The 90% confidence interval for lnCmax was outside the [80-125] limits. However, the fed study was conducted prior to the issuance of the Food Effect Bioequivalence Study Guidance (issued 01/2003), therefore, the confidence interval criteria was not applied to the PK parameters.

Table 22 Nimodipine Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Test Treatment

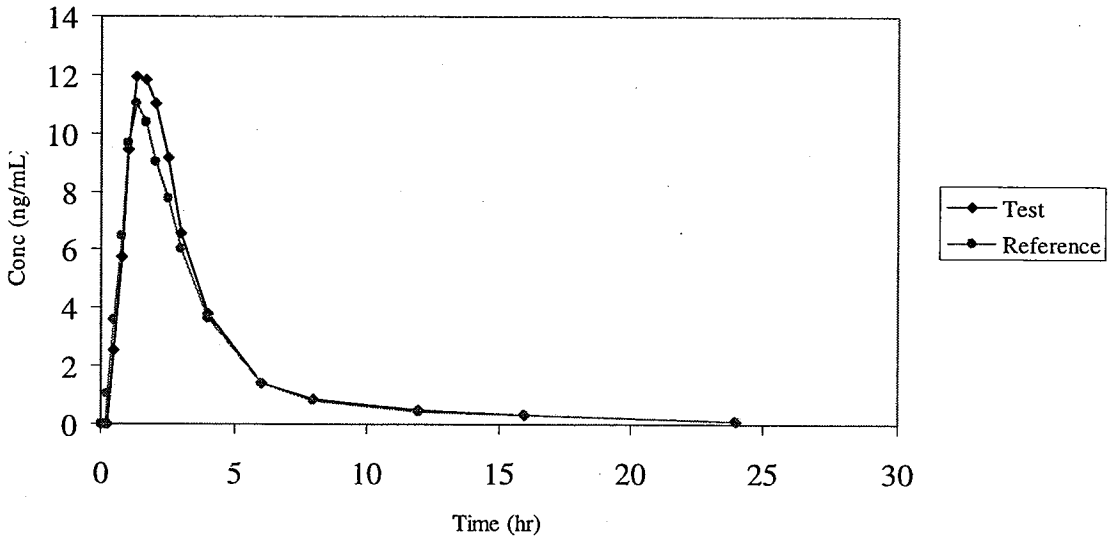
Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	45	0.000	0.000	0.000	0.000
Hour0.167	45	0.000	0.000	0.000	0.000
Hour0.25	45	0.026	0.085	0.000	0.410
Hour0.50	45	2.552	5.273	0.000	30.140
Hour0.75	45	5.754	9.029	0.100	53.880
Hour1	45	9.433	9.285	0.320	46.580
Hour1.333	45	11.956	8.639	0.980	35.760
Hour1.667	45	11.804	7.218	2.310	34.200
Hour2	45	11.041	6.349	3.490	39.870
Hour2.50	45	9.155	5.373	2.230	35.290
Hour3	45	6.568	3.617	1.650	21.060
Hour4	45	3.774	2.335	1.070	12.420
Hour6	45	1.421	0.879	0.370	5.050
Hour8	45	0.889	0.459	0.250	2.620
Hour12	45	0.476	0.244	0.120	1.100
Hour16	45	0.332	0.170	0.080	0.820
Hour24	45	0.127	0.095	0.000	0.320

Reference Treatment

Time	N	Mean	Std Dev	Minimum	Maximum
Hour0	45	0.000	0.000	0.000	0.000
Hour0.167	45	0.006	0.039	0.000	0.258
Hour0.25	45	1.023	5.941	0.000	39.890
Hour0.50	45	3.603	7.438	0.090	37.070
Hour0.75	45	6.481	6.822	0.230	33.830
Hour1	45	9.636	7.416	0.700	27.840
Hour1.333	45	10.994	8.446	0.610	44.590
Hour1.667	45	10.348	6.579	1.340	34.240
Hour2	45	9.012	5.078	1.520	24.820
Hour2.50	45	7.745	5.089	1.960	23.490
Hour3	45	6.018	3.907	1.660	20.650
Hour4	45	3.629	2.146	1.000	10.200
Hour6	45	1.399	0.966	0.400	4.970
Hour8	45	0.798	0.354	0.220	1.760
Hour12	45	0.409	0.189	0.110	0.990
Hour16	45	0.301	0.167	0.000	0.810
Hour24	45	0.119	0.100	0.000	0.380

Figure 2

Nimodipine Mean Plasma Concentrations
Nonfasting Study



B. Formulation Data

Components/Grade	Pharmaceutical function	Per Capsules	
		mg	%
Capsule Fill			
Nimodipine	Active	30	2.7
Glycerine, USP			
Peppermint oil, NF			
Polyethylene Glycol (b) (4) **NF			
Total weight		1115.0	100.0
Capsule Shell			
Gelatin, NF			
Glycerine, USP			
Sorbitol (b) (4)			
(b) (4)			
Glycerine, USP (Kosher)			
Titanium Oxide, USP			
Total shell amount		439.3	100

* To be confirmed with the scale up run
*Quantitative disclosure of the capsule shell ingredients in Bannar Pharmacaps, Inc.'s drug Master File # 14194
** The concentration of the inactive ingredient, polyethylene glycol exceeds the maximum concentration of the inactive ingredient previously approved by the agency in an orally administered drug product.

Comments: The inactive ingredients are within the approved IIG ranges except for PEG (b) (4) The pharmacological/toxicological consult by the Division of Cardio-Renal Drug Products, HFD-110, has the following overall comments concerning the toxicological data submitted by the firm:

" Overall, the material presented shows that PEG (b) (4) given orally has relatively low toxicologic potential. The studies from 1954 and 1952 were conducted to different standards than those used today. Difficulties common to both dosing studies are smaller group sizes than are typically used today and less detail than is currently provided for the reviewer to come to an independent conclusion. Nevertheless, the studies provided animals with substantial exposure to the test material with minimal adverse results apparent in the data.

The 90 day study (1991) was more helpful. The study was designed to look at potential effects upon the kidney, the primary organ of toxicological concern. Rats were dosed with 1128, 2820 or 5460 mg/kg/day. Loose feces were seen at MD and HD with a mild weight effect, 3% less weight gain, compared to control at the HD.

With some inconsistencies, drug-treated animals consumed on average more water than did the control animals. This was apparent from week 2 to the end of the dosing period and was not maintained during the recovery period. There were no significant hematology findings and no indications of altered renal function in the clinical chemistry data. Both sexes showed increased specific gravity of urine.

The tables that summarized the histopathological findings were not provided. Organ weight tables showed no difference in absolute kidney weight. As a percentage of body weight there was a statistically significant increase in the kidney weights but without dose dependence. The biological significance, if any, is uncertain. Overall, the material presented shows that when PEG (b) (4) is given daily to rats at doses up to 5 g/kg there are minimal discernible effects."

Based on the above consult comments, the DBE considers the PEG (b) (4) amount present in the test formulation to be safe and acceptable.

(For the full consult report, see Attachment on page 24 of this review. Please note the consult was erroneously referred to the current ANDA as 76-760, instead of 76-740)

C. Dissolution Data

Testing Conditions:

Source of Method	Firm
Medium	0.5% Sodium Dodecyl Sulfate
Volume (mL)	900
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm
Firm's proposed specification	NLT (b) (4) (Q) in 30 minutes

Table 23

Sampling Time (min)	Test Product, Strength 30 mg Lot No. XPP0204004			Reference Product, Strength 30 mg Lot No. 25P0039		
	Mean	%CV	Range	Mean	%CV	Range
10	17	52	(b) (4)	49	45	(b) (4)
20	90	8.3		94	2.3	
30	94	2.6		97	1.6	
45	95	3.6		97	1.8	

D. SAS Output

1. Fasting Study:

76740fast.txt

2. Nonfasting Study:

76740fed.txt

E. Pharmacological/Toxicological Consult on PEG (b) (4) Content of Test Formulation

76_740pharmtoxc
onsultnimodipine.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-740 APPLICANT: Pliva, Inc.

DRUG PRODUCT: Nimodipine Capsules, 30 mg

The Division of Bioequivalence has completed its review and has the following deficiencies:

We agree with your proposed dissolution method as follows:

> The dissolution testing should be conducted in 900 mL of water with 0.5% SDS, at 37°C using USP Apparatus II(paddle) at 50 rpm.

However, we have recommended the following specification for the test product based on the data submitted.

> Not less than (b) (4) Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The recommended specification is different from your proposed specification. Please provide your response to our recommendation concerning the dissolution specification.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:ANDA 76-740
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ SNerurkar
HFD-617/ A. Sigler
HFD-650/ D. Conner 2/8/05

2/8/05

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE
DISSOLUTION - INCOMPLETE

Submission date: 05-14-04

1. FASTING STUDY (STF)
Clinical: MDS Pharma Services
Analytical: MDS Pharma Services

Strength: 30 mg
✓ **Outcome: IC**

2. NONFASTING STUDY (STP)
Clinical: MDS Pharma Services
Analytical: MDS Pharma Services

Strength: 30 mg
✓ **Outcome: IC**

3. STUDY AMENDMENT (STA) Telephone Amendment dated 12-10-04 providing information concerning reassay samples & SOP

Strength: 30 mg
X **Outcome: IC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable **NC** - No credit

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # :	76-740	SPONSOR : Pliva, Inc.
DRUG AND DOSAGE FORM :	Nimodipine Capsules	
STRENGTH(S) :	30 mg	
TYPES OF STUDIES :	Fasting and Nonfasting Studies (30 mg)	
CLINICAL STUDY SITE(S) :	MDS Pharma Services	
ANALYTICAL SITE(S) :	MDS Pharma Services	

STUDY SUMMARY :	Acceptable
DISSOLUTION :	Acceptable
WAIVER REQUEST:	N/A

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic Yes New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes__ No X
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes __X__
Amendment Date: April 1, 2005

PROJECT MANAGER: Keri Suh, Pharm.D. _____ DATE: 04/14/05

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH:

INITIAL : _____ DATE : 4/14/05

TEAM LEADER : Nerurkar Shrinivas, Ph.D. BRANCH:

INITIAL : _____ DATE : 4/14/2005

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : _____ DATE : 4/14/05