CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-009

BIOEQUIVALENCE

Block ... Y.1 X

Isosorbide Dinitrate
40 mg SR Tablet
ANDA # 40-009
Reviewer: A.J. Jackson
WP# 40009SC.997

Inwood Laboratories
New York, New York
Submission Date:
~~September 2, 1997~~ JUNE 26, 1998
October 14, 1998
October 22, 1998

Review of Correspondence for a Single Dose Fasting Study and a Post-Prandial Study

Background

The firm submitted a single dose fasting study on April 14, 1995 to support the approval of their product. The study was found to be incomplete due to analytical deficiencies and a change in the bioequivalence lot between the multiple dose study (completed in 1991) and the single dose study. A food study is a requirement for all SR products and the firm had not submitted a food study for review. The firm responded to those deficiencies and submitted a food study for review. Several deficiencies were still unresolved related to the single dose and food study. The current submission is the firm's response to the deficiencies related to the single dose fasting study and the results of the food study.

Comment #1: Your submitted information on manufacturing is acceptable however, the dissolution data for the single dose study lots 94020A (106% dissolution in 12 hours), 96064E (99% mean dissolution in 12 hours) appear to be quite different in dissolution from the multiple dose lot 88125D (83% dissolution in 12 hours) and therefore fails to establish the required similarity between the lots. If you have no satisfactory explanation for this difference then the multiple dose study will have to be repeated using a lot similar to lots 94020A and 96064E.

Response:

The 83% dissolution after 12 hours for lot 88125D does not completely describe the dissolution history of this lot, as the

value was derived from testing performed prior to the initiation of stability evaluation. At time of release (5/20/88), 104% dissolution in 12 hours was obtained. Prior to use of the material in the clinic (ca. 10/29/89 to 11/24/89), lot 88125D was tested from bulk storage and found to have 97% dissolution in 12 hours. Three separate dissolution tests were performed prior to the start of the clinical evaluation; the average of these gives 97% dissolution in 12 hours. Moreover, tablets from a concurrent stability study of lot 88125D packaged in HDPE bottles (100 count) stored at 25-30°C/ambient gave 103% dissolution in 12 hours at roughly the end of the clinical study (test date 11/16/89). From a review of all data available for lot 88125D (including stability studies), 26 determinations from May 1988 through February 1991 show an average of 95% dissolution in 12 hours with 7.4% RSD.

Values of the 12 hour dissolution results for Lot #88125D tested at different times are listed below:

Test Date	**Percent Dissolution in 12 Hours**
05-20-88	104
11-11-88	83
07-27-89	98
09-19-89	95
10-10-89	97

FDA Reply: The firm's response is acceptable.

Comment #2. You have done numerous sample repeats with the reason being "re-assayed due to sample value not fitting pharmacokinetic profile. Since the kinetics of isosorbide dinitrate are highly variable, one can not be certain what is a 'pharmacokinetic outlier" (ie concentration appearing to increase or decrease rapidly during log-linear phase). Therefore you should use the original assay value for all samples deemed to not have followed the "pharmacokinetic profile " for the 2-way cross over fasting study and for the 3way crossover food study. Once these values have been substituted, the pharmacokinetic and statistical analysis of the data should be repeated.

Response:

Values for all "reassayed due to sample value not fitting pharmacokinetic profile" and all other reassay values have been replaced with the original assay values and the pharmacokinetic and statistical data analyses have been repeated for both studies, the 2-way crossover fasting study (TR/1700/0004) and the 3-way crossover food study (ISD-PKA-9601-000).

Exhibit 1 shows tables from the original report of the 2-way crossover fasting study (TRJ 1700/0004). These tables list the concentrations by subject and period for Isosorbide Dinitrate, Isosorbide-2-Mononitrate and Isosorbide-5-Mononitrate. Subject numbers without a suffix indicate the original concentration values. Subject numbers which include the suffix "R1" or "R2" indicate samples for which one (RI) or two (R2) re-assays were done. A second re-assay was carried out if the original value and the first re-assay were different by more than 20%. The pharmacokinetic analysis presented in this document is based on the original concentration values.

Exhibit 2 displays the results of the pharmacokinetic analysis of the 2-way crossover fasting study (TR/1700/0004) using the original concentration values as described above. The calculated pharmacokinetic parameters include Cmax, $AUCO_{0-t}$, $AUC_{0-\infty}$ and T_{max}. The data are presented in a manner which was suggested in Comment #4. Tables 1 to 6 list the individual and mean concentrations of Isosorbide-5-Mononitrate, Isosorbide-2-Mononitrate and Isosorbide Dinitrate for each subject according to treatment. Tables 7 to 11 list individual and mean values for the pharmacokinetic parameters of Isosorbide-5-Mononitrate and ratios of these parameters as suggested in Comment #4. Table 12 summarizes the results of Isosorbide-5-Mononitrate by listing the average values (arithmetic and geometric) as well as the corresponding 90% confidence intervals. Tables 13 to 18 and Tables 19 to 24 present the results of the pharmacokinetic analysis of Isosorbide-2-Mononitrate and Isosorbide Dinitrate, respectively, in a manner analogous to that for Isosorbide-5-Mononitrate.

The GLM output of the statistical analysis for Isosorbide-5-Mononitrate, Isosorbide-2Mononitrate and Isosorbide Dinitrate is included in Exhibit 3.

In-text Table 1 summarizes the 90% confidence intervals for the pharmacokinetic parameters Cmax, $AUCO_{0-t}$, $AUC_{0-\infty}$ for the 2-way crossover fasting study (TR/ 1700/0004). The column "Original Concentrations" presents the 90% confidence intervals for the pharmacokinetic parameters Cmax, $AUCO_{0-t}$, and $AUC_{0-\infty}$ based on concentration data which do not include any re-assays. The column "Re-assayed Concentrations" displays the results from the previously submitted analysis, based on concentration data which include re-assayed concentrations (these data may be found in the submission, dated April 14, 1995, in Table VII on page 33 [Isosorbide-5-Mononitrate], in Table IV on page 374 [Isosorbide Dinitrate] and in Table VIII on page 381 [Isosorbide-2-Mononitrate] of the original report). Copies of these tables are provided here in Exhibit 4 for convenience.

As can be seen from in-text Table 1 the results from the analysis using original concentration data and results from the analysis using re-assayed concentrations are in good agreement. Therefore, the analysis of the original concentrations without any re-assayed concentration values did not change the overall conclusion that Inwood ISDN ER tablets were bioequivalent to Wyeth/Ayerst Isordil Tembids ISDN tablets under fasted conditions when administered as a single dose.

Table 1. Comparison of PK Data based on Original and Reassay Concentration Values for the 2-Way Crossover Fasting Study (TR/1700/0004).

	90% confidence intervals, based on log-transformed data	
PK Parameter	**Original Concentrations 5-ISMN**	**Reassayed Concentrations**
Cmax, (ng/mL)	94-103	94-103
AUC0-t, (ng-hr/mL)	103-108	103- 108
AUC0-inf (ng-hr/mL)	104-109	104-109

	2-ISMN	
Cmax (ng/mL)	86-97	87-96
AUC0-t, (ng-hr/mL)	103-110	103-110
AUC0-inf (ng-hr/mL)	103-110	103-109
	ISDN	
Cmax, (ng/mL)	57-69	57-69
AUC0-t (ng-hr/mL)	94-111	93-110
AUC0-inf (ng-hr/mL)	n/a	n/a

n/a = not available.

Exhibit 5 presents the bioanalytical report for the 3-way crossover food study (ISD-PKA-9601 -000) as provided by PPD Pharmaco, Inc. Revisions from the original bioanalytical report are indicated by the label "Revised Page 05/01/98" at the bottom and the label "Revised Page" at the top of each revised page. The concentrations of Isosorbide-2-Mononitrate (Table #11), Isosorbide-5-Mononitrate (Table #12) and Isosorbide Dinitrate (Table #13) are listed by subject and period. Subjects with the suffix R or R1 denote replacement subjects. The suffix RI indicates that the first replacement subject (R) had to be replaced by another subject. Tables # 14, # 15 and #16 list all the samples for which PPD Pharmaco, Inc. had conducted re-assays. The column "Assay 1" indicates the original value, the column "Assay 2" the first re-assay and the column "Assay 3" the second reassay.

Exhibit 6 displays the results of the pharmacokinetic re-analysis of the 3-way crossover food study (ISD-PKA-96-01-000) presented in a manner according to the suggestions made in Comment #4. The calculated pharmacokinetic parameters include Cmax, AUC0-t,, AUC0-inf and Tmax. Tables 25 to 33 list the individual and mean concentrations of Isosorbide-5Mononitrate, Isosorbide-2-Mononitrate and Isosorbide Dinitrate for each subject according to treatment. Tables 34 to 38 present the individual and mean values for the pharmacokinetic parameters for Isosorbide-5-Mononitrate as well as the ratios of these parameters as suggested in Comment #4. Table 39 summarizes the results for Isosorbide-5-Mononitrate by displaying the average values for the pharmacokinetic parameters as well as the

corresponding 90% confidence intervals. Tables 40 to 45 and Tables 46 to 51 display the results for Isosorbide-2-Mononitrate and Isosorbide Dinitrate, respectively, in an analogous manner.

Exhibit 7 displays the GLM output of the statistical analysis for the 3-way crossover food study (ISD-PKA-96-01-000). Statistical analyses were carried out using the model suggested in Comment #6 ("complete" model) and a "collapsed" model (the Variable Group was deleted from the model). In the case of the complete model the least square means were not estimable because the two groups were unbalanced (20 subjects in Group 1 versus 4 subjects in Group 3). Therefore, the "collapsed" model was used to calculate the 90% confidence intervals.

In-text Table 2 summarizes the 90% confidence intervals for the pharmacokinetic parameters Cmax, AUC0-T and AUC0-inf for the 3-way crossover food study (ISD-PKA-96-01-000). The column "Original Concentrations" presents the 90% confidence intervals for the pharmacokinetic parameters Cmax, AUC0-T, and AUC0-inf, based on the original concentration data which do not include any re-assays. The presented 90% confidence intervals are based on the "collapsed" model. The column "Re-assayed Concentrations" displays the results from the analysis previously submitted, based on concentration data which include reassayed concentrations (these data may be found in the submission, dated September 2, 1997, in Table VIII on page 705 [Isosorbide-5-Mononitrate], Table XII on page 715 [Isosorbide-2-Mononitrate] and in Table XVI on page 725 [Isosorbide-Dinitrate] of the original report). Copies of these tables are provided here in Exhibit 8 for convenience.

As can be seen from in-text Table 2, the results of the analysis of the original concentrations without any re-assayed concentration values did not change the overall conclusion that Inwood ISDN ER tablets were bioequivalent to Wyeth/Ayerst Isordil Tembids ISDN tablets under fed conditions when administered as a single dose.

Table 2.Comparison of PK Data based on Original and Reassay Concentration Values for the 3-Way Crossover Food Study (ISD-PKA-96-01-000).

PK Parameter	90% confidence intervals, based on log-transformed data	
	Original Concentrations	Reassayed Concentrations
	IS-5-MN	
Cmax, (ng/mL)	97-110	97-110
AUC0-t (ng-hr/mL)	97- 103	97-103
AUC0-inf (ng-hr/mL)	96-103	97- 103
	IS-2-MN	
Cmax (ng/mL)	94-109	95-110
AUC0-t, (ng-hr/mL)	98- 105	99-106
AUC0-inf (ng-hr/mL)	98-105	99-106
	ISDN	
Cmax (ng/mL)	85-114	86-114
AUC0-t(ng-hr/mL)	100-118	100-115
AUC0-inf(ng-hr/mL)	82-97	100 - 115*

*In the original report this 90% confidence interval was given which is based on AUC0-t values instead of AUC0-inf data.

Overall, the analysis of the concentration data from both studies, the 2-way crossover fasting study (TR/1700/0004) and the 3-way crossover food study (ISD-PKA-96-01-000), using original concentration data without any re-assayed concentration values did not change the overall conclusions from these studies, that Inwood ISDN ER tablets are bioequivalent to Wyeth/Ayerst Isordil' Tembids' ISDN tablets under fasted and fed conditions when administered as a single dose.

FDA Reply: The firm's response is acceptable -

Comment#3. The 2-ISMN assay for the post-prandial study indicated that there was an interfering peak in the chromatograms of several subjects. Unfortunately, the chromatograms submitted were not from the subjects such as 19, 20, 27 and 28 whose chromatograms were noted by the firm to contain the interfering peak. You should submit chromatograms for all subjects with interfering peaks.

Response:

All chromatograms with interfering peaks are submitted in Exhibit 9. Interfering peaks were observed for sample chromatograms, quality control chromatograms and standard curve chromatograms.

A total of eleven (11) sample chromatograms were identified as having interferences. These include sample chromatograms from Subjects 18, 19, 20 and 24. In each of these cases the following chromatograms are provided:

1. The sample chromatogram containing the interference.
2. Both, a quality control and a standard chromatogram from the same analytical run as the interference chromatogram to indicate the retention times of the analytes.
3. The duplicate sample chromatogram demonstrating no interference.
4. Both, a quality control and a standard chromatogram from the same analytical run as the duplicate sample chromatogram.

In addition, interfering peaks were noted for three (3) low quality control samples which were analyzed in the same analytical run as Subjects 4, 12 and 24. In each of these three cases the following chromatograms are provided:

1. The low quality control sample containing the interference.
2. The standard chromatogram and the medium quality chromatogram from the same run.

Also, interfering peaks were noted for eight (8) standard curve chromatograms of Isosorbide2-Mononitrate for Runs 12, 19, 20, 27 and 28. In these cases the chromatograms with the interferences are provided.

FDA Reply: The firm's response is acceptable.

Comment #4. You should submit the following tables on a diskette in a Word Perfect format after completing the reanalysis of your data. Separate tables should be submitted for the single dose-fasting and post-prandial studies. The tables are:

a. Table of mean plasma concentration data,
b. Table of mean parameters including geometric means (e.g. from LS means),
c. Table containing the individual subject test to reference ratios for Cmax, Tmax, AUC(0-t), AUC (0-inf).
d. Table listing the AUC(0-t)/AUC(0-inf) ratio for each subject.

Response:

Tables for (a) mean plasma concentration data, (b) Cmax Tmax AUC0-t, and AUC0-inf, (c) mean pharmacokinetic parameters, and (d) the ratio of AUC0-t to AUC0-inf are presented in Exhibit 2 for the 2-way crossover fasting study (TR/1700/0004) and in Exhibit 6 for the 3-way crossover food study (ISD-PKA-96-01 -000) and are provided on a diskette in WordPerfect format following this letter.

FASTING STUDY RESULTS

Table 1.

Study TR/1700/0004 - Summary of Mean Results of Isosorbide-5-Mononitrate Pharmacokinetic Parameters.

PARAMETERS	Isosorbide Dinitrate 40 mg ER Tablets (Forest/Inwood) LOT #94020A	ISORDIL® TEMBIDS® LOT #9940510
C_{max} (ng/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	227.39 ± 32.35 93 - 103% 98%	232.49 ± 38.55
C_{max} (ng/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	225.08 94 - 103% 98%	229.32
$AUC_{(0-t)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a]	2785.35 ± 442.18 103-108%	2632.01 ± 385.16

Rel. Bioavail.[b]	106%	
$AUC_{(0-t)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	2751.64 103 - 108% 106.2%	2604.38
$AUC_{(0-\infty)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	2891.51 ± 481.68 104 - 109% 107%	2711.80 ± 407.85
$AUC_{(0-\infty)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	2853.08 104 - 109% 106%	2682.36
T_{max} (hours)	5.18 ± 0.98	3.89 ± 1.11

a. 90% Confidence interval two one-sided t procedure for Inwood Lab relative to Isordil® Tembids® under fed condition, based on either un-transformed data (arithmetic means) and log-transformed data (geometric means).

b. Test /Reference

Table 2 **Study TR/1700/0004** - Summary of Mean Results of Isosorbide-2-Mononitrate Pharmacokinetic Parameters.

PARAMETERS	Isosorbide Dinitrate 40 mg ER Tablets (Forest/Inwood) LOT #94020A	ISORDIL® TEMBIDS® LOT #9940510
C_{max} (ng/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	41.60 ± 6.32 84 - 95% 89%	46.52 ± 9.90
C_{max} (ng/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	41.09 86 - 95% 90%	45.54
$AUC_{(0-t)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	307.22 ± 45.75 103 - 109% 106%	288.62 ± 41.69
$AUC_{(0-t)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	304.02 103 - 110% 106%	285.74
$AUC_{(0-\infty)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	316.46 ± 50.11 104 - 110% 107%	295.49 ± 42.35
$AUC_{(0-\infty)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	312.75 103 - 110% 107%	292.60

T_{max} (hours)	4.50 ± 1.23	2.88 ± 1.11

a 90% Confidence interval, two one-sided t procedure for Inwood Lab relative to Isordil® Tembids® under fed condition, based on either un-transformed data (arithmetic means) and log-transformed data (geometric means).

b. Test /Reference

Table 3. **Study TR/1700/0004** - Summary of Mean Results of Isosorbide Dinitrate Pharmacokinetic Parameters.

PARAMETERS	Isosorbide Dinitrate 40 mg ER Tablets (Forest/Inwood) LOT #94020A	ISORDIL® TEMBIDS® LOT #9940510
C_{max} (ng/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	8.32 ± 2.96 52 - 71% 61%	13.58 ± 5.65
C_{max} (ng/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	7.89 57 - 69% 63%	12.54
$AUC_{(0-t)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	37.66 ± 13.95 96 - 112% 104%	36.22 ± 12.13
$AUC_{(0-t)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	35.25 94 - 111% 102%	34.48
$AUC_{(0-\infty)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavail.[b]	50.16 ± 22.05 83 - 125% 104%	48.10 ± 24.30
$AUC_{(0-\infty)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavail.[b]	46.46 90 - 122% 105%	44.36
T_{max} (hours)	2.88 ± 1.86	1.48 ± 0.76

a 90% Confidence interval, two one-sided t procedure for Inwood Lab relative to Isordil® Tembids® under fed condition, based on either un-transformed data (arithmetic means) and log-transformed data (geometric means).

b. Test /Reference

FOOD STUDY RESULTS

Table 4. - Summary of Mean Results for Isosorbide-5-Mononitrate.

PARAMETERS	Isosorbide Dinitrate 40 mg ER Tablets (Inwood Lab) Lot # 96064E Fasted Condition	Isosorbide Dinitrate 40 mg ER Tablets (Inwood Lab) Lot # 96064E Fed Condition	ISORDIL® TEMBIDS® (Wyeth/Ayerst) Lot # 9960528 Fed Condition
C_{max} (ng/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	265.4 ± 59.06	287.9 ± 57.23 97 - 110 104% 108%	277.6 ± 44.89
C_{max} (ng/mL) (Geometric) 90% C.I, Rel. Bioavailability[b] Rel. Bioavailability[c]	259.60	280.67 97 - 110 102% 108%	274.11
$AUC_{(0-t)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	3180.45 ± 459.96	3105.56 ± 445.1 97 - 103 100% 98%	3097.25 ± 326.95
$AUC_{(0-t)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	3148.41	3075.63 97 - 103 100% 98%	3081.44
$AUC_{(0-\infty)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	3333.39 ± 480.51	3253.87 ± 476.80 97 - 103 100% 98%	3253.41 ± 356.35
$AUC_{(0-\infty)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	3299.92	3221.02 96 - 103 100% 98%	3235.55
T_{max} (hours)	4.92 ± 1.18	5.58 ± 0.50	5.04 ± 0.86

a 90% Confidence interval, two one-sided t procedure for Inwood Lab relative to Isordil® Tembids® under fed condition, based on either un-transformed data (arithmetic means) and log-transformed data (geometric means).

b. Test Fed /Reference Fed

c. Test Fed/Test Fasted

Table 5. Summary of Mean Results for Isosorbide-2-Mononitrate.

PARAMETERS	Isosorbide Dinitrate 40 mg ER Tablets (Inwood Lab) Lot # 96064E Fasted Condition	Isosorbide Dinitrate 40 mg ER Tablets (Inwood Lab) Lot # 96064E Fed Condition	ISORDIL® TEMBIDS® (Wyeth/Ayerst) Lot # 9960528 Fed Condition
C_{max} (ng/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	51.0 ± 10.26	63.5 ± 11.07 95 - 108 101% 125%	62.7 ± 11.88
C_{max} (ng/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	50.08	62.57 94 - 109 101% 125%	61.66
$AUC_{(0-t)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	361.73 ± 57.24	374.38 ± 51.81 98 - 105 102% 103%	368.27 ± 49.69
$AUC_{(0-t)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	357.43	370.98 98 - 105 102% 104%	365.12
$AUC_{(0-\infty)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	369.71 ± 57.68	380.41 ± 51.88 98 - 104 101% 103%	376.06 ± 50.80
$AUC_{(0-\infty)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	365.38	377.41 98 - 105 101% 103%	372.84
T_{max} (hours)	3.75 ± 0.99	4.79 ± 1.02	5.04 ± 0.88

a 90% Confidence interval, two one-sided t procedure for Inwood Lab relative to Isordil® Tembids® under fed condition, based on either un-transformed data (arithmetic means) and log-transformed data (geometric means).

b. Test Fed /Reference Fed

c Test Fed/Test Fasted

Table 6 - Summary of Mean Results for Isosorbide Dinitrate.

PARAMETERS	Isosorbide Dinitrate 40 mg ER Tablets (Inwood Lab) Lot # 96064E Fasted Condition	Isosorbide Dinitrate 40 mg ER Tablets (Inwood Lab) Lot # 96064E Fed Condition	ISORDIL® TEMBIDS® (Wyeth/Ayerst) Lot # 9960528 Fed Condition
C_{max} (ng/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	13.4 ± 6.22	23.6 ± 8.04 84 - 111 97% 176%	24.3 ± 9.33
C_{max} (ng/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	12.26	22.39 85 - 114 99% 183%	22.71
$AUC_{(0-t)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	51.02 ± 16.70	73.02 ± 22.81 101 - 117 109% 143%	66.95 ± 19.15
$AUC_{(0-t)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	48.18	69.62 100 - 118 109% 144%	64.20
$AUC_{(0-\infty)}$ (ng·hr/mL) (Arithmetic) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	56.72 ± 22.25	77.91 ± 19.88 89 - 101 96% 138%	81.43 ± 15.85
$AUC_{(0-\infty)}$ (ng·hr/mL) (Geometric) 90% C.I.[a] Rel. Bioavailability[b] Rel. Bioavailability[c]	52.70	69.19 82 - 97 89% 131%	78.10
T_{max} (hours)	2.48 ± 1.32	4.15 ± 1.38	3.96 ± 1.30

a *90% Confidence interval, two one-sided t procedure for Inwood Lab relative to Isordil® Tembids® under fed condition, based on either un-transformed data (arithmetic means) and log-transformed data (geometric means).*

b. Test Fed /Reference Fed

c *Test Fed/Test Fasted*

FDA Reply: The firm's response is acceptable.

Comment #5. You did not give the name of the person responsible for conducting the analytical assays for the post-prandial study.

Response:

The name of the person responsible for the analytical assays is Diane M. Muehlmann. Her curriculum vitae is attached in Exhibit 10. She is a scientist in the Bioanalytical Department of PPD Pharmaco, Inc. Also included in Exhibit 10 is the curriculum vitae of Randal D. O'Rourke, the Laboratory Director of the Bioanalytical Group.

FDA Reply: The firm's response is acceptable.

Comment#6. You conducted your post-prandial studies on the following dates

Group I August 21 August 28 September 4
Group II September.10 September11 September25

Therefore the study involved 6 dosing periods. However, the statistical model used by the firm contained only 3 periods. The revised data for the study should be analyzed with the following model in order to account for all periods. The model is:

*Y= GRP SEQ SUBJ (GRP *SEQ) PER (GRP) TRT*

Response:

The suggested statistical model was used for the analysis of the 3-way crossover food study (ISD-PKA-96-0 1 -000). The resultant GLM output is included in Exhibit 7. The results were also included in the response to Comment #2. Confidence intervals (90%) were calculated for the pharmacokinetic parameters Cmax, AUCO-T,and AUC0-inf for Isosorbide-5-Mononitrate, Isosorbide-2-Mononitrate and Isosorbide Dinitrate. Due to the inclusion of the Variable Group into the "complete" model, least square means could not be obtained because the two groups were unbalanced (20 subjects in Group I versus 4 subjects in Group 3). Therefore, 90 % confidence intervals were calculated based on the "collapsed" model (the Variable Group was dropped from the analysis [Y = SEQ SUBJ (SEQ) PER TRT]). Therefore for each

pharmacokinetic parameter the output from the two models (complete versus collapsed model) is presented. A. summary of the results and a comparison with the originally submitted values can be found in in-text Table II. As can be seen from the re-analysis of the data there are no differences in the results when using original concentration data or reassayed concentration data. Thus, the conclusion, based on the reanalysis of the 3-way crossover food study (ISD-PKA-96-01-000), is that Inwood ISDN ER tablets are bioequivalent to Wyeth/Ayerst Isordill Tembids' ISDN tablets under fed conditions when administered as a single dose.

Comments:

1. The 90 % confidence intervals for the fasting study are within the acceptable limits.

2. The food study was done as a 3 period, 6 sequence study. Analysis of the data using the model :

Y=GRP SEQ SUBJ(GRP*SEQ) PER(GRP) TRT

resulted in LSMEANS being non-estimable. The use of the model :

Y=SEQ SUBJ(SEQ) PER TRT

also resulted in LSMEANS being non-estimable. This was due to only 4 subjects/sequence. Therefore due to these computational problems the food study was evaluated based upon arithmetic means which were well within the limits of 80-120%.

Recommendation:

The single dose fasting bioequivalence study conducted by Inwood Laboratories on its Isosorbide Dinitrate Extended release tablets, lot # 94020A,comparing it to Wyeth-Ayerst's Isordil Tembids, 40 mg sustained release tablet, lot 9940510 has been found to be acceptable by the Division of Bioequivalence. The multiple dose study had been found to be acceptable based upon the December 15, 1993 submission. The single dose post-prandial study conducted by Inwood Laboratories on its Isosorbide Dinitrate Extended release tablets, lot 96064E, comparing it to Wyeth-Ayerst's Isordil Tembids 40 mg sustained release tablets, lot # 9960528 has also been found to be acceptable by the Division of Bioequivalence. The study demonstrates that Inwood Laboratories' Isosorbide Dinitrate Extended release tablets, lot # 94020A is bioequivalent to the reference product to Wyeth-Ayerst's Isordil Tembids 40 mg sustained release tablets.

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 11/29/98

Concur: Date: 11/30/98

Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

cc:

Addendum to the Review

History of Review

The firm submitted their first study on April 4, 1991 which was done as a single dose four-way crossover using three test lots (88124D, 88125D and 86400J). The reference lot was 1880126. The study met the CI for only Cmax and AUC(0-T) for 5-ISMN and AUC(0-T) for 2-ISMN. This study was done in only 8 subjects. Therefore the study was found to be unacceptable. The multiple dose study submitted on the same date was later found to be acceptable based upon **5-ISMN** only. This was based upon a regulatory decision by the Office of Generic Drugs in 1993. A new single dose fasting study was submitted on April 14, 1995 on lot 94020A since the lot used for the multiple dose study was no longer available. The firm established the similarity between the two lots(i.e. 88124D-single dose and 94020A-multiple dose) based upon dissolution and manufacturing information. On September 2, 1997 the firm submitted a post-prandial study which was found to be acceptable based upon the correspondence in the current September 1997 amendment.

fc-009 submitted 4/4/91

SD study

Table VII
Summary of Statistical Parameters

Parameter	ISDN 90% Confidence Interval
Cmax	(29 83)
AUC(0-T)	(102 128)

Parameter	2-ISMN 90% Confidence Interval
Cmax	(66 99)
AUC(0-T)	(96 109)

Parameter	5-ISMN 90% Confidence interval
Cmax	(86 106)
AUC(0-T)	(94 104)

Adverse Effects

The major adverse effect recorded was mild headache. These have been summarized in table VIII.

TABLE VIII

SUMMARY OF ADVERSE REACTIONS

PROTOCOL NO. R/IC040/0488 (FRENCH #697-1)

Subject No.	Phase	Formulation	Adverse Reaction	Treatment
	I	Inwood A	mild to moderate headache	none
	I	Isordil	mild to moderate headache	none
	II	Inwood B	mild to severe headache	acetaminophen 325 mg
	I	Inwood B	moderate headache	none
	II	Inwood A	mild headache	none
	II	Inwood C	mild headache	none
	I	Inwood C	mild headache	none
	II	Isordil	mild headache	none
	II	Inwood B	mild headache	none

Isosorbide Dinitrate
40 mg SR Tablet
ANDA # 40-009
Reviewer: A.J. Jackson
WP# 40009A.997

Inwood Laboratories
New York, New York
Submission Date:
September 2, 1997
October 31, 1997

Addendum To Review

The dissolution specification set forth in the review of September 2, 1997 for this product was:

> The dissolution testing should be conducted in 900 ml of simulated gastric fluid pH 1.2 for 1 hour.
>
> The medium should be changed to 900 ml of simulated intestinal fluid pH 7.5 for hours 1-12.
>
> The test product should meet the following specifications:

	Time	Amount Dissolved
pH 1.2	1 hr	
pH 7.5	3 hr	
	6 hr	
	12 hr	

Following consultation with the Division of Chemistry the final specification was changed to:

The test product should meet the following specifications:

	Time	Amount Dissolved
pH 1.2	1 hr	
pH 7.5	3 hr	
	6 hr	
	12 hr	

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 11/29/98

11/30/98

Isosorbide Dinitrate
40 mg SR Tablet
ANDA # 40-009
Reviewer: A.J. Jackson
WP# 40009SC.997

Inwood Laboratories
New York, New York
Submission Date:
September 2, 1997
October 31, 1997

Review of Correspondence for a Single Dose Fasting Study and Review of a Post-Prandial Study

Background

The firm submitted a single dose fasting study on April 14, 1995 to support the approval of their product. The study was found to be incomplete due to analytical deficiencies and a change in the bioequivalence lot between the multiple dose (completed in 1991) and the single dose study. A food study is a requirement for all SR products and the firm had not submitted a food study for review. The current submission is the firm's response to the deficiencies related to the single dose fasting study and the results of the food study.

FDA Comment: 1 i.

The lot size and the formulation for the bio-lot# 94020A were not specified in the bioequivalency section of this submission and are required for review. In future submissions this data should be included in the bioequivalency sections of the application.

Response:

Included, as part of Attachment 7, is the batch size and formulation (see page 375) for **Lot** # 94020A.

FDA Reply: The firm's response is acceptable and the information is appended to this review in Appendix I.

Comment: 1 ii.

Chromatograms for 20% of the subjects in the study were not included and are required for review. In future submissions this data should be included in the bioequivalency section of the

submission.

Response:

We enclose for your review copies of chromatograms for seven (7) subjects, which represents 25% of the total subjects in the study. Those for subjects 8, 21 and 23 are newly submitted. Those for subjects 5, 6, 15 and 16 were included in our April 14, 1995 submission and are provided for your convenience. (Attachment 1).

FDA Reply: The firm's reply is satisfactory.

Comment: 1 iii.

An explanation should be given for the relevance of the Reference Lot # 9940553 discussed in the study #1497 page 1822 since Reference Lot # 9940510 was mentioned in the Protocol page 1846.

Response:

The lot number of the reference product Isordil® Tembids® 40mg ER Tablets of Wyeth-Ayerst Laboratories used in this study [Forest Study # R/1700/0004, Biovail Corporation International, Study # 1497 (Clinical portion)] was 9940553. The lot number of the reference product initially selected to be used in the study, as mentioned in the main section of the protocol (pages 51 and 1846), was 9940510. However, when determined within one month of the initiation of the study, the total content of the active moiety Isosorbide Dinitrate of the test product (Inwood Laboratories, Lot # 94020A) to be used in the study was found to be beyond the acceptance limit of ± 5% of the reference product. Due to the difference in total content of the active moiety, the reference product was changed to Lot # 9940553. Subsequently, this change had been amended and approved through Amendment D dated September 9, 1994 which was attached at the end of the protocol section. Thus, actually the reference product with lot # 9940553 was used in the study as documented in the Supplies Receipt Record (Attachment 2). Please note that in some places of the technical report (pages 11 and 10), tables (pages 22, 33, 39, 40, 373, 374, 380, and 381) and the footer of the SAS output the reference lot number was inadvertently mentioned as 9940510 instead of 9940553.

FDA Reply: The firm's explanation is satisfactory.

Comment: 1 iv.

Please supply a detailed SOP for the conduct of the stability studies in plasma for the subject samples.

Response:

Attachment 3, volume 2 contains SOPs relevant to the stability studies of plasma samples.

FDA Reply: The information provided by the firm for their SOP on stability is satisfactory.

Comment: 1 v.

Please submit for review the long term stability data for the plasma samples.

Response:

Attachment 4 contains long-term stability data for the plasma samples.

FDA Reply: The data from the stability study was for approximately 6 months, November 10, 1995 to May 9, 1996. Data tables containing the stability data are presented in appendix II. The data is satisfactory.

Comment: 1 vi.

The individual plasma data for ISDN were all zero at time zero. Therefore, you should explain the origin of the 0.05 ng/mL value for ISDN at time zero in table III page 373.

Response:

As reported in Table IA, page 368, the plasma concentrations of

Isosorbide Dinitrate (ISDN) at time 0 hr (pre-dose) for all subjects were 0.00 ng/mL except for Subject #26. Subject #26 had an ISDN concentration of 1.31 ng/mL. Therefore, the mean ± SD was 0.05 ±0.25 ng/mL as reported in Table III, page 373.

Subject #26 had this detectable concentration (1.31 ng/mL) at 0 hr during Period II. This was not a carryover effect from Period I since in Period I, his ISDN concentration was lower than the limit of quantitation (treated as zero) at 9 hr and at all subsequent blood sampling times up to 30 hr.

For your convenience, pages 368 and 373 are included here as Attachment 5.

FDA Reply: Inwood's laboratories explanation is acceptable.

Comment: 1 vii.
Incomplete comparative dissolution data was supplied; please submit for review the values for the individual tablets, their range, percent CV and method of analysis.

Response:

Included as Attachment 6 are the Analytical Reports for Forest Lot #s 88125D and 94020A, and the reference product (Isordil E-R Tablet, USP 40 mg) Lot # 9940553 for the individual tablets, as well as a summary of the dissolution data for all three lots used in the bio-studies.

FDA Reply: The dissolution data is presented in Dissolution Table 1 is acceptable. The Division of Bioequivalence has also proposed the following dissolution specifications for the product:

Specifications:

Comment: 2 i General Comment:

As a condition of approval extended-release tablets require three in vivo bioequivalence studies as follows:

A single dose, two-period, two-treatment, two-sequence, crossover study under fasting conditions, comparing equal doses of the test and reference product;

A single dose, randomized, three-treatment, three-period, six-sequence, crossover, limited food effects study, comparing equal doses of the test product administered under fasting conditions with those of the test and reference products administered immediately after a standard breakfast: and

A multiple dose, steady-state, randomized, two-treatment, two-period, two-sequence crossover study under fasting conditions comparing equal doses of the test and reference formulations.

Details about each study may be found in the Office of Generic Drugs guidance entitled "Guidance Oral Extended (Controlled) Release Dosage Form In vivo Bioequivalence and In vitro Dissolution Testing" Dated September 9, 1993.

Response:

We acknowledge your comment. Please note that the following three biostudies have previously been submitted to this application:

"A Comparative Four-way Directional Bioavailability Study of Sustained-release Isosorbide Dinitrate Tablets in Human Volunteers." (# R/1 C040/0488, submitted 4/4/91)

"A Multiple Dose, Two-way Study to Evaluate the Relative Bioavailability of Isosorbide Dinitrate CR Tablets in Human Volunteers." (# R/1700/0002, submitted 4/4/91)

"A Two-Way, Crossover, Single Dose, Bioavailability Study of Isosorbide Dinitrate ER Tablets 40 mg in Fasted Human Volunteers." (# R/1700/0004, submitted 4/14/95)

FDA Reply: The Division of Bioequivalence acknowledges the receipt and review of these studies.

Comment: 2 ii.

The multiple dose study on lot # 88125 was previously submitted, however, the current single dose study has been done using lot #

94020A. Generally, all required studies should be conducted on test product from the same lot. Since the submitted studies were conducted with product from different lots, you must establish equivalency between Lots 88125 & 94020A by providing manufacturing procedures, process equipment, formulation, dissolution and other pertinent information both in vitro and in vivo to establish equivalence.

Response:

Attachment 7 includes the following comparative information for lots # 88125 (used in the multiple dose study), and 94020A (used in the single dose study) (See response to August 15, 1996 communication which follows our response to comment 2 iii): 1) Composition Comparison Statement; 2) Manufacturing procedures and equipment used, a flow chart comparison, and executed batch records; 3) Analytical data, including dissolution; and 4) Stability. The data from all comparisons support the equivalency of the two lots of ISDN ER Tablets, USP 40 mg used in the bio-studies.

FDA Reply: The submitted information on manufacturing is acceptable however, the dissolution data for single dose study lots 94020A(106% dissolution in 12 hrs), 96064E(99% mean dissolution in 12 hrs)appear to be quite different in dissolution from the multiple dose lot 88125D(83% dissolution in 12 hrs) and therefore fails to establish the required similarity between the lots. If the firm has no satisfactory explanation for this difference then the multiple dose study will have to be repeated using a lot similar to lots 94020A and 96064E.

Comment: 2 iii.

A non-fasting study is required as a condition of approval and has not been submitted.

Response:

This submission contains the results of a non-fasting bioequivalence study (Study # TR/ISD-PKA-96-01-000) (Appendix 1).

FDA Reply: The Division of Bioequivalence acknowledges the receipt of the post-prandial study for review.

August 15, 1996 communication

General Comments:

1. The Office understands that you intend to conduct a non-fasting study as requested in our March 3, 1996 correspondence. In the correspondence we identified that a different lot (#88125) was used in the multiple dose study than the lot in the single dose study (# 94020A). The correspondence specified that generally, all required studies should be conducted on test product from the same lot, and thus, you must establish equivalence between Lots 88125 & 94020A by providing manufacturing and other pertinent information to establish equivalence.

It is noted that you intend to use lot # 96064E for the required non-fasting study, and that this lot is different than those used in either the fasting study or multiple dose study. If you conduct the non-fasting study with this lot, you will be required to establish equivalence between Lots 88125, 94020A and 96064E by providing manufacturing procedures, process equipment, formulation, dissolution and other pertinent information to establish equivalence. Unless these parameters are deemed to be unchanged the bioequivalence studies will not be acceptable.

Response:

Both these issues are addressed in Attachment 7, where data are given for lot#s 88125D, 94020A and 96064E, showing that there is equivalence among all three lots in regard to manufacturing procedures, process equipment, formulation, dissolution and other pertinent information (including potency).

Included in this submission as Appendices 1 through 11 is the study report entitled "A Three-way Crossover, Single Dose, Bioequivaleney Study of Isosorbide Dinitrate ER Tablets, 40 mg in Fasted and Fed Male Volunteers (Report # TR/ISD-PKA-96-01-000)."

This study was conducted to evaluate the rate and extent of absorption of a single dose of Isosorbide Dinitrate ER Tablets, 40mg (Inwood) compared to Isordil® Tembids® 40mg ER Tablets (Wyeth-Ayerst) in normal, healthy, non-smoking male volunteers under fed

conditions. The study also investigated the effect of food on the rate and extent of absorption of Isosorbide Dinitrate ER Tablets, 40mg (Inwood). Twenty-four subjects completed the study.

The study clearly demonstrated that Inwood Isosorbide Dinitrate ER Tablets, 40mg (Lot #96064E) are bioequivalent to Isordil® Tembids® 40mg tablet (Lot #9960528) of Wyeth-Ayerst with respect to bioavailability of 5-ISMN as well as 2-ISMN and ISDN under fed conditions. The relative bioavailability of Inwood Isosorbide Dinitrate ER Tablets, 40mg (Lot #96064E) compared to Isordil® Tembids® 40mg tablet (Lot #9660528) were within 80-120% for IS5MN as well as IS2MN and ISDN under fed conditions.

The study also demonstrated that food has an effect on the absorption of ISDN as evidenced by the delayed time to peak (Tmax) for IS5MN as well as IS2MN and ISDN. The rate of absorption (Cmax) increased for 5-ISMN as well as 2-ISMN and ISDN. However, the extent of absorption (AUC) were similar between fasting and fed conditions for 5-ISMN and 2-ISMN respectively. The extent of absorption for the ISDN moiety increased after administration with food.

Single Dose Post-Prandial Study

INTRODUCTION

Isosorbide Dinitrate (ISDN) is an antianginal drug with effects to dilate both arterioles and venules. ISDN is well absorbed following oral administration but has a low bioavailability, 19 to 25%, as a result of its rapid metabolism in the liver (first-pass), blood vessels and gut wall.

ISDN is readily metabolized by hepatic and extrahepatic glutathione transferases to two pharmacologically active metabolites, isosorbide-2-mononitrate (2-ISMN) and isosorbide-5-mononitrate (5-ISMN). These metabolites have pharmacologic properties that are qualitatively similar to ISDN but with lesser potency.

5-ISMN is the primary metabolite of ISDN in man and animals. It has been observed that 5-ISMN is responsible for many of the hemodynamic effects of ISDN since 5-ISMN appears to be as clinically effective as ISDN. Others have demonstrated in man with digital plethysmography that 5-ISMN has a greater vasodepressor effect than ISDN when given in equal doses. Following ISDN administration the pharmacodynamic effects paralleled the plasma concentrations of 5-ISMN but had no apparent relationship with the concentrations of ISDN. The duration of the cardiovascular action of ISDN has been attributable to the prolonged presence of the active metabolites rather than to ISDN. It has been suggested that the 'long-acting' properties of ISDN are the result of the sustained, elevated concentrations of 5-ISMN.

Inwood Laboratories has developed Isosorbide dinitrate extended release 40 mg tablets which it has compared to Wyeth-Ayerst's Isordil® Tembids® 40 mg tablets following single dose and multiple dose administrations to show that its product is bioequivalent to Tembids® 40 mg tablets.

Objectives

The purpose of this study is to evaluate the rate and extent of absorption of a single dose Isosorbide Dinitrate ER Tablets, 40 mg (Lot # 96064E, Inwood Laboratories. Inc.) compared to Isordil®

Tembids® 40 mg ER Tablets (Lot # 9960528, Wyeth-Ayerst) in normal, healthy, non-smoking male volunteers under fed conditions. The study also investigates the effect of food on the rate and extent of absorption of Isosorbide Dinitrate ER Tablets, 40 mg (Inwood).

Methods:

The study was conducted by South Florida Bioavailability Clinic Miami, Florida under the direction of Stephen R. Scheinman, M.D. The samples were analyzed by
Pharmacokinetic and statistical analysis was done at . The study was begun on August 28, 1996 and completed on September 26, 1996. Sample analysis began after September 26 and was completed by October 30, 1996. Therefore total sample storage time was approximately 7 weeks.

Study Design

This was a single dose, three-way crossover, randomized study in twenty four (24) normal, healthy, non-smoking male volunteers under fasted and fed conditions. Due to replacement of dropped subjects, thirty (30) subjects were included in the study, and the study was conducted in three groups.

Subject Population

Thirty (30) healthy, nonsmoking male subjects between 18 and 35 years of age were enrolled into the study; twenty-four (24) subjects completed the trial. Subjects were institutionalized volunteers such as students, members of the civic groups and members of the community at large.

Characterization of Volunteers

All subjects body weights were normal (±15%) for their heights, according to the guidelines in standard weight tables, Metropolitan Life Insurance Company Statistical Bulletin, 1983.

Subjects were judged in good health following a complete medical history, physical examination, electrocardiogram and the battery of clinical laboratory tests listed below:

Biochemical Profile: serum calcium, urea nitrogen, glucose, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase, SGOT, SGPT, cholesterol, triglycerides, globulins, electrolytes (sodium, potassium and chloride) and creatinine.

Hematology: hemoglobin, hematocrit, white blood cell total and differential counts, red blood cell count and morphology, platelet count and sedimentation rate.

Urinalyses: specific gravity, pH, protein, glucose, ketone, bilirubin, blood, microscopic examination, drugs of abuse (at the time of enrollment only).

The physical examination, clinical tests and electrocardiogram were repeated at the end of the study prior to discharge.

Subject Inclusion Criteria

Prospective subjects were included in the study if they had fulfilled all of the following criteria:

- Subjects had provide written informed consent.
- Subjects must be healthy young males within 18 and 35 years of age.

Subjects must be non-smoking (never smoked or have not smoked within the past two years).

Subjects must have, at the time of screening, normal vital signs, serum chemistry, hematology, urinalysis, negative Anti HIV 1, HbsAg and Rapid Plasma Reagin (RPR) or VDRL. Any values that fell outside the normal range that were judged to be not clinically significant by the Principal Investigator and the Sponsor were marked as such and initialed by the Principal Investigator in the case report forms.

Subjects must have a normal 12-lead ECG at screening. A subject with an abnormal pre-study ECG was accepted into the study if both the Investigator and the Sponsor agree that the abnormality is not clinically significant and the Investigator documents it, as such, in the case report form.

Subject Exclusion Criteria

Prospective subjects were excluded from enrollment in this study for any of the following reasons:

Subjects incapable of understanding the informed consent.

Subjects who had a known sensitivity to isosorbide dinitrate or to organic nitrates.

Subjects who, in the opinion of the examining physician, had a clinically significant cardiovascular, gastrointestinal, renal, hepatic, pulmonary or hematologic disease state.

Subjects who had a history of a cardiac conduction defect, heart block or sinus bradycardia. For the purpose of this protocol, sinus bradycardia will be defined as a heart rate $\leq$ 50 beats per minute as determined by ECG.

Subjects who had a history of clinically significant hypotension or hypertension (unless currently stable and normotensive without concomitant medication and acceptable to both Principal Investigator and Sponsor).

Subjects with a blood pressure at screening that exceeds 160 mmHg systolic or 90 mmHg diastolic. Subjects with a blood pressure at screening lower than 100 mmHg systolic or 60 mmHg diastolic in any pre-study examination or a heart rate below 50 beats per minute.

A subject with a confirmed ECG PR interval of greater than 0.20 seconds at pre-screen.

Subjects who had consumed alcohol or xanthine containing beverages or foods within 48 hours prior to dosing.

Subjects who had a history of alcohol or substance abuse within the last 5 years.

Subjects who had a history of acute narrow angle glaucoma.

Subjects who tested positive for drugs of abuse.

Subjects with any other clinical condition which might affect the absorption, distribution, biotransformation or excretion of the drugs.

Subjects who have participated in any other clinical investigation using an experimental drug or requiring repeated blood draws within 30 days of the start of this study.

Subjects who participated in a blood donation program within the past 60 days.

Subjects who have a history of migraine headaches.

Subject is an employee or relative of an employee at the Clinical Research Organization (CRO).

Informed Consent

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

Institutional Review Board Approval

The investigator obtained written approval of the protocol by an independent Institutional Review Board.

Subject Demographics

The subjects who completed the study had a mean age of 29 years and mean body weight of 72 kg. A summary of the individual subjects characteristics who completed the study is presented in Appendix III.

Study Drugs

The products employed in the study were:

1. Test: Inwood Laboratories 40 mg Isosorbide Dinitrate ER tablet, Lot # 96064E, potency 100.7%, lot size

2. Reference product: Isordil^{R} 40 mg tablet, Lot # 9960528, potency 95.7%.
Expiration date for the reference was February 1998.

There was a 7 day washout between doses.

All test and reference products were supplied to the investigator by Forest Laboratories, New York, NY. The test product was Isosorbide Dinitrate ER tablets, 40 mg (Inwood Laboratories, Inc, Lot # 96064E) and the reference product was Wyeth-Ayerst's Isordil ® Tembids® 40 mg tablets (Lot # 9960528).

STUDY DESIGN AND DRUG ADMINISTRATION

This study was a randomized, three-way crossover, single dose bioavailability study in thirty (30) normal male volunteers following oral administration under fasted and fed conditions; twenty-four (24) subjects completed the trial. Period I of the study started with twenty-four (24) subjects but twenty-three (23) subjects completed the period. Subject no. 21 withdrew consent and was dropped from the study. Period II started with twenty-one (21) subjects who completed Period I, and all of these subjects completed Period II. Subjects 1 and 9 did not return to Period II. Subject 22 did not return for Period III dosing. Thus, Period III of the study started with twenty (20) subjects who successfully completed the study. Twenty (20) subjects (Subject # 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 23 and 24)who completed all three periods were considered to be in Group 1. Two (2) additional subjects 1R and 9R were used as replacement subjects for Subjects 1 and 9, respectively. However, subject 1R was dropped due to an intercurrent illness (consistent elevated alanine transaminase) and subject 9R withdrew consent and was dropped from the study. These two subjects (1R and 9R) are considered to be in Group 2. Four (4) additional subjects 1R1, 9R1, 21R and 22R were enrolled as replacement subjects for Subjects 1R, 9R, 21 and 22, respectively. These subjects received the same treatment sequence as subjects 1, 9, 21 and 22 respectively. These 4 subjects (Subjects 1R1, 9R1, 21R and 22R) completed all three periods and are considered to be in Group 3. Therefore, the study was considered to be completed by administering the drugs in two (2) groups, Group 1 and Group 3 (the 2 subjects who enrolled in Group 2 dropped out).

The following three (3) treatments were administered during the study:

Treatment A:
One (1) Isosorbide dinitrate ER Tablet, 40 mg (Inwood Laboratories, Inc.) administered with 240 mL of water following a 10 hour overnight fast.

Treatment B:
One (1) Isosorbide dinitrate ER Tablet, 40 mg (Inwood Laboratories, Inc.) administered with 240 mL of water following a standardized, high fat breakfast.

Treatment C:
One (1) Isordil® Tembids® 40 mg tablet (Wyeth Ayerst Laboratories) administered with 240 mL of water following a standardized, high fat breakfast.

The standardized breakfast consisted of:

Two fried eggs
One slice of toast with a pat of butter (10 g) and jelly (20 g)
Two strips of bacon
4 ounces (= 113 g) of hash brown potatoes
8 ounces (= 227 mL) of whole milk.
180 mL of orange juice
The treatments were administered according to the following randomization scheme:

	Treatment for Period Number		
Subject Numbers	I	II	III
5, 11,17,24	A	B	C
3, 8, 13, 20	A	C	B
2, 9R1, 14, 23	B	C	A
1R1, 12, 16,21R	B	A	C

4, 10, 15, 19	C	A	B
6, 7, 18, 22R	C	B	A

A complete listing of the treatments administered and the randomization of subjects can be found in Appendix IV.

After an overnight fasting for at least 10 hours or following a standardized, high fat breakfast, all subjects received one (1) Isosorbide Dinitrate ER tablet, 40 mg according to the above randomization at 8:00 am. The treatment periods were separated by seven days. Subjects remained ambulatory or seated upright and awake for the first four hours following drug administration and did not engage in strenuous activity at any time during the study.

Diet and Fluid

All treatments were administered with 240 mL of water. No food was allowed for 4 hours post-dose, but water was allowed *ad libitum* until 1 hour prior to drug administration and 1 hour after dosing.

With the exceptions noted above, standardized bland low-fat meals were provided to all subjects beginning at 1200 and 1700 hour and a snack was provided at approximately 2100 hour on each day of institutionalization. On day 2, breakfast was provided to all subjects beginning at 0900 hour. The meals and snacks were free of xanthine-containing compounds (including caffeine) with less than 20 grams of fat each and were identical during each study period.

Vital Signs Monitoring

Vital signs (blood pressure and pulse rate) were measured and recorded with the subject seated in an upright position and on the same arm throughout the study. To insure adherence to this requirement, all vital signs were taken on the right arm. This procedure was followed for screening and for vital sign collection at the following times:

0.0 (predose), 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0, 12.0, 16.0, 20.0, 24.0, and 30.0 hours after the 0800 hour dose administration.

On those occasions when meal times coincided with the vital signs and blood sampling schedule, the vital signs were measured first, then the blood samples were drawn prior to meals.

Each time the vital signs were recorded, subjects were questioned as to their adverse event experience.

As per protocol, subjects with a blood pressure at screening that exceeded 160 mmHg systolic or 90 mmHg diastolic were excluded from study participation. All enrolled study subjects met these requirements.

Appendix V contains the blood pressure data. The table lists instances in which blood pressures were found to be in the low end of normal range or outside the range of 100/60 mmHg. In the estimation of the Principal Investigator it was not deemed necessary to repeat the measurements.

Concomitant Medications

No concomitant medication was necessary during the study. Subjects were instructed also not to take any drugs for at least 14 days prior to and during the course of the study. They were specifically reminded that this included aspirin, ibuprofen, acetaminophen, Bufferin®, Excedrin®, Anacin®, vitamin preparations, cough syrup, etc.

Collection and Processing of Blood Samples

Fifteen (15) blood samples (5 mL each) were obtained during each period of the study as follows: 0.0 (predose), 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0, 12.0, 16.0, 20.0, 24.0 and 30.0 hours after drug administration. Blood samples were collected by a qualified phlebotomist using one 5 mL 'siliconized' Vacutainer® tube containing tripotassium EDTA. The tubes were kept on ice until centrifuged. A maximum of 265 mL of blood were collected during the course of this study (including pre-study and post-study clinical analysis) from each subject.

Vacutainer® tubes containing blood samples were inverted to mix the blood with the content of Vacutainer® tube and placed upright in the centrifuge and centrifuged at 3500 rpm for 15 minutes. Approximately 2.5 mL of plasma at each time point was harvested and transferred into polypropylene culture tubes. All plasma samples were frozen and stored upright at -70°C.

Polypropylene tubes were labeled at the site with a code number that corresponded to period number, subject number and blood draw time. The code numbers were provided by Inc. All blood samples were collected within 1 minute of the scheduled sample collection time.

Shipment of Plasma Samples

Samples were packaged by subject number, and shipped via overnight courier on sufficient dry ice to keep them frozen to:

11735

The samples were logged in and an audit check was performed at the BioAnalytical laboratories of . The frozen samples were stored at -70°C in the Bioanalytical Lab until shipped under frozen condition (dry ice) to:

where the plasma samples were assayed for ISDN, IS2MN and IS5MN concentrations.

Analytical Method

Plasma samples were analyzed by , using a suitable analytical method and to determine levels of isosorbide dinitrate and its major metabolites, IS2MN and IS5MN, in plasma. The validation report including data demonstrating the accuracy, linearity,

reproducibility and precision of the analytical procedure, together with a standard calibration curve and data exhibiting stability under freeze-thaw conditions.

ISOSORBIDE DINITRATE

Assay sensitivity:
The assay was linear over the range of 1.0 ng/mL to 60 ng/mL. The limit of sensitivity of the assay was defined as 1.0 ng/mL, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 6.0% at a concentration of 1.0 ng/mL and 2.19% at 60 ng/mL.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 107% at a concentration of 4.0 ng/mL and 102% at 50.0 ng/mL.

2- **ISOSORBIDE MONONITRATE**

Assay sensitivity:
The assay was linear over the range of 1.0 ng/mL to 60 ng/mL. The limit of sensitivity of the assay was defined as 1.0 ng/mL, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 6.0% at a concentration of 1.0 ng/mL and 2.85% at 60 ng/mL.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 112% at a concentration of 4.0 ng/mL and 103% at 50.0 ng/mL.

5- **ISOSORBIDE MONONITRATE**

Assay sensitivity:
The assay was linear over the range of 5.0 ng/mL to 300 ng/mL. The limit of sensitivity of the assay was defined as 5.0 ng/mL, with values less than this reported as zero.

Precision and Reproducibility:
Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 4.0% at a concentration of 5.0 ng/mL and 3.87% at 300 ng/mL.

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. The accuracy was 101% at a concentration of 20.0 ng/mL and 104% at 250.0 ng/mL.

Assay Validation

Recovery:

The recoveries of ISDN, 2-ISMN and 5-ISMN and the internal standard extracted from plasma were determined by comparison of the extracts to solutions of the pure drugs subjected to the matrix effect.
Six replicate standards at 4.00 ng/mL, 15.0 ng/mL, and 50.0 ng/mL for ISDN and 2-ISMN and at 20.0 ng/mL, 75.0 ng/mL, and 250.0 ng/mL for 5-ISMN were spiked and subsequently extracted as described using the confidential method.
The recovery of the internal standard was determined at the concentration used in the confidential method.
In addition, eighteen blank plasma samples were extracted with the above spiked samples. The blank plasma samples were also assayed according to the confidential method, with the exception that just prior to injection, they were spiked with ISDN, 2-ISMN, 5-ISMN and the internal standard to match the above

concentrations (six at each concentration). The samples prepared from the blanks are designated as the pures.

The samples were injected onto a stem as Set E4, starting with the lowest concentration and pairing the extracted and pure samples.
The percent recovery for each extracted standard was calculated from the standard peak height divided by the average peak height of the six respective pure samples, multiplied by 100. The recovery of the low, medium and high standards are 91.7%, 81.6% and 87.0% for ISDN; 62.3%, 58.3% and 63.5% for 2-ISMN and 62.2%, 54.8% and 60.9% for 5-ISMN. The recovery of the internal standard used for ISDN and 2-ISMN is 55.8%, while the recovery of the internal standard for 5-ISMN is 55.8%. All coefficients of variation were under 15%. Recovery data are presented in Volume 11 pages 2830-2832.

Freeze/Thaw of Plasma: To determine the effect of freezing and thawing on the concentrations as of ISDN, 2-ISMN and 5-ISMN in human plasma, several tubes each of the low, medium and high controls were designated as freeze/thaw controls. These controls were subjected to subsequent freezing and thawing. Controls at each level subjected to two and three freeze/thaw cycles were analyzed in triplicate in Set 28 of Study No.WARS-5139AA. Freeze/thaw cycle one was not analyzed. The SOP accepts data if the freeze/thaw cycle control mean calculates within twenty percent of the low control theory and fifteen percent of the medium and high control theory. The mean percent differences from theory for ISDN ranged from -10.5% to -14.8%, from -8.0% to -8.7% and from -1.8% to 2.6% for the low, medium and high freeze/thaw concentrations, respectively. The mean percent difference from theory for the 2-ISMN medium freeze/thaw concentration is 4.7% for both cycles. The mean percent differences from theory for 2-ISMN ranged from 4.3% to 5.0% and from 0.2% to 5.0% for the low and high freeze/thaw concentrations, respectively. The mean

percent differences from theory for 5-ISMN ranged from 10.0% to 13.0%, from 11.6% to 11.9%, and from 0.8% to 5.8% for the low, medium and high freeze/thaw concentrations, respectively.

Based on these data, 3 freeze/thaw cycles did not affect the calculated concentrations of ISDN, 2-ISMN and 5-ISMN in human plasma. The data presented in Volume 11 pages 2833-2841 are acceptable.

Bench Top Stability: To demonstrate that the samples, once extracted, are stable under injection conditions, the following experiment was performed. Three aliquots of the medium control were extracted on November 13, 1995 and stored under injection conditions. The extracts were injected on November 15, 1995 with Set 28 of Study No. WARS-5139A. Data are acceptable based upon the SOP if the bench top control mean calculates within fifteen percent of the medium control theory. The mean percent differences from theory are 2.0%, 6.7% and 6.7% for ISDN, 2-ISMN and 5-ISMN, respectively.

Based on these data presented in Volume 11 page 2842, extracted samples stored under injection conditions are stable for at least 48 hours are acceptable.

Matrix Bench Top Stability: To demonstrate that the compounds are stable in the matrix at room temperature (e.g. freezer malfunction), the following experiment was performed. On November 13, 1995, four medium control aliquots were removed from the freezer and stored at room temperature on the laboratory bench. On November 14, 1995, four additional medium control aliquots were removed from the freezer and stored at room temperature on the laboratory bench. These eight medium control aliquots were extracted on November 15, 1995 along with Set 28 of Study No. WARS-5139A, so that four aliquots were thawed for 24 hours and four aliquots were thawed for 48 hours prior to extraction. The data were calculated and are reported using the individual curve for Set 28 of Study-No. WARS-5 ,9A. Data are acceptable based upon the SOP if the matrix bench top control mean calculates within fifteen percent of the medium control theory. The mean percent differences from theory for ISDN are -2.7% and -4.0% for the 24 Hour and 48 Hour matrix bench top concentrations, respectively. The mean percent differences from theory for 2-ISMN are 13.3% and 28.0% for the 24 Hour and 48 Hour matrix bench top

concentrations, respectively. The mean percent differences from theory for 5-ISMN are 12.3% and 6.7% for the 24 Hour and 48 Hour matrix bench top concentrations, respectively. In addition, trending effects are evaluated as follows. The mean value of the regular medium controls analyzed in Set 28 is defined as the initial time (To). Analyte in matrix is considered stable at room temperature if the matrix stability control mean calculates within fifteen percent of To. The mean percent differences from To for ISDN were 5.0% and 3.6% for the 24 Hour and 48 Hour matrix bench top concentrations, respectively. The mean percent differences from To for 2-ISMN were 8.3% and 22.3% for the 24 Hour and 48 Hour matrix bench top concentrations, respectively. The mean percent differences from To for S-ISMN were 1.6% and -3.5% for the 24 Hour and 48 Hour matrix bench top concentrations, respectively.

Based on these data, ISDN and 5-ISMN in human plasma were stable at room temperature for at least 48 Hours and 2-ISMN in human plasma is stable at room temperature for 24 Hours.
The results presented in Volume 11 pages 2843-2845 are acceptable.

Pharmacokinetic Analysis.

The maximum plasma drug concentrations, Cmax, for ISDN, IS2MN and IS5MN were determined by observation as the peak concentration for each treatment for each subject. The time of maximum concentration, Tmax, was determined as the time corresponding to Cmax. The areas under the plasma ISDN, IS2MN and IS5MN concentration *versus* time curves (AUCo.t) were calculated by using the linear trapezoidal rule.The first-order rate constant, lambda z, describing the terminal decline of ISDN, IS2MN and IS5MN following oral administration was estimated by WinNonlin computer software using log-linear regression of the terminal linear phase of concentration-time curves.
The area under the plasma concentration *versus* time curve from time 0 to inf (AUC0-inf) was calculated by adding the extrapolated area Ct(last)/lambda z to AUC(0-t) where Ct(last) is

the last non-zero concentration and lambda z is the terminal elimination rate constant of ISDN, IS2MN and IS5MN.
The relative bioavailability of ISDN, IS2MN and IS5MN for the test product (Inwood Laboratories) compared to the reference product Isordil® Tembids® was determined as the test/reference (T/R) ratio of mean values for AUC(0-t) and AUC(0-inf).

STATISTICAL ANALYSIS

Statistical analyses were performed using Statistical Analysis System (SAS) version 6.11(SAS Institute, Inc. North Carolina) for microcomputer. Analysis of Variance (ANOVA) was performed using General Linear Models Procedure (GLM).The 90% confidence intervals were estimated using two one-sided t procedure was performed according to Schuirmann.

Results

Since the firm has to reanalyze their data due to analytical problems summary parameters for ISDN, 2-ISMN and 5-ISMN will not be presented until that analysis is complete.

Table 1.Isosorbide Dinitrate plasma levels (± sd) for the subjects that received 40 mg of the test and reference formulations after a high fat meal.

Test-Fasting TREATMENT A			TEST-FOOD TREATMENT B		Reference-Food TREATMENT C	
Time	Mean	SD	Mean	SD	Mean	SD
0	0.0		0.0		0.0	
0.5 hr	5.25	3.54	0.99	1.29	1.40	1.28
1.0 hr	8.05	3.03	3.16	3.80	4.18	4.41
1.5 hr	9.98	5.13	5.57	5.09	7.05	6.47
2.0 hr	10.28	4.91	7.34	5.97	9.72	10.90
3.0 hr	8.75	3.52	9.36	5.91	12.37	10.18
4.0 hr	6.92	2.80	13.29	8.42	12.10	6.47
5.0 hr	7.32	6.07	18.71	8.10	14.62	9.71
6.0 hr	4.36	2.67	10.77	8.64	7.44	3.92
9.0 hr	1.18	1.55	1.21	0.95	1.06	1.11
12 hr	0.05	0.25	0.10	0.34	0.05	0.23
16 hr	0.00	0.00	0.00	0.00	0.00	0.00
20 hr	0.00	0.00	0.00	0.00	0.00	0.00
24 hr	0.00	0.00	0.00	0.00	0.00	0.00
30 hr	0.00	0.00	0.00	0.00	0.00	0.00

Table 2.2-Isosorbide Mononitrate plasma levels (± sd) for the subjects that received 40 mg of the test and reference formulations after a high fat meal.

Test-Fasting TREATMENT A			TEST-FOOD TREATMENT B		Reference-Food TREATMENT C	
Time	Mean	SD	Mean	SD	Mean	SD
0	0.0	0.00	0.0	0.00	0.0	0.00
0.5 hr	7.56	4.28	1.02	1.19	1.27	1.29
1.0 hr	17.96	4.95	4.43	4.50	5.55	4.72
1.5 hr	28.96	8.20	9.59	8.17	11.72	8.94
2.0 hr	36.69	10.20	15.24	11.50	18.86	15.17
3.0 hr	45.10	9.62	26.85	14.31	33.19	23.04
4.0 hr	46.25	8.84	42.37	13.73	45.13	15.06
5.0 hr	44.77	11.40	55.74	18.42	55.37	15.59
6.0 hr	37.54	10.46	48.88	19.91	49.46	10.06
9.0 hr	19.49	6.44	23.83	6.77	21.99	4.93
12 hr	7.21	3.59	10.15	3.07	8.57	3.83
16 hr	2.56	1.45	3.25	1.28	2.78	1.22
20 hr	0.93	1.21	0.98	0.78	1.60	2.92
24 hr	0.05	0.22	0.04	0.20	0.00	0.00
30 hr	0.00	0.00	0.00	0.00	0.00	0.00

Table 3.Isosorbide 5-Mononitrate plasma levels (± sd) for the subjects that received 40 mg of the test and reference formulations after a high fat meal.

Test-Fasting TREATMENT A			TEST-FOOD TREATMENT B		Reference-Food TREATMENT C	
Time	Mean	SD	Mean	SD	Mean	SD
0	0.0	0.0	0.0	0.0	0.0	0.0
0.5 hr	25.97	16.16	2.09	4.18	5.19	8.79
1.0 hr	67.07	20.43	14.50	16.98	21.40	4.41
1.5 hr	114.91	30.37	34.55	30.91	45.62	36.50
2.0 hr	152.64	37.94	57.16	45.06	75.50	56.14
3.0 hr	209.19	38.27	110.85	60.45	138.35	84.17
4.0 hr	231.99	39.99	183.01	62.34	195.15	66.44
5.0 hr	253.76	62.79	250.88	81.33	267.37	38.21
6.0 hr	233.40	45.35	275.87	52.60	259.91	43.72
9.0 hr	191.08	39.20	207.15	36.24	198.08	29.72
12 hr	124.04	36.23	149.05	27.50	134.69	33.17
16 hr	82.37	20.62	88.80	20.02	84.98	13.89
20 hr	58.24	21.51	54.02	15.43	62.02	26.94
24 hr	34.09	10.17	34.02	9.79	34.01	6.90
30 hr	17.43	6.43	16.93	4.75	17.52	4.28

Adverse Events

The most commonly reported side effect was headache, with a total of 54 reported during the trial. Dizziness was reported by 9 subjects. All other adverse events occurred exclusively in one subject and in single incidents. The total number of adverse

events reported during the study was 71. These are summarized by period in Appendix VI.

Sample Repeats

The sample repeats are numerous and are listed in Appendix VII.

Dissolution

The dissolution study for ISDN was done as follows:

Apparatus:	Paddle, 50 RPM
Medium:	900 ml Simulated Gastric, pH 1.2
	900 ml Simulated Intestinal, pH 7.5
No. of Units Analyzed:	12
Specifications: (Proposed by Firm)	[redacted]

Assay:

Deficiencies:

1.The firm has done numerous sample repeats with the reason being " reassayed due to sample value not fitting pharmacokinetic profile." Since the kinetics of isosorbide dinitrate is highly variable, one can not be certain what is a "pharmacokinetic outlier" (ie concentration appearing to increase or decrease rapidly during log-linear phase. Therefore the firm should use the original assay value for all samples deemed to not have

followed the "pharmacokinetic profile"for the 2-way crossover fasting study and for the 3-way crossover food study. Once these values have been substituted, the pharmacokinetic and statistical analysis of the data should be repeated.

2.The 2-ISMN assay for the post-prandial study indicated that there was an interfering peak in the chromatograms of several subjects. Unfortunately, the chromatograms submitted were not from the subjects such as 19, 20, 27 and 28 whose chromatograms were noted by the firm to contain the interfering peak. You should submit chromatograms for all subjects with interfering peaks.

3.The firm should submit the following tables on a diskette in a word perfect format after they have completed the reanalysis of their data. Separate tables should be submitted for the single dose fasting and post-prandial studies. The tables are:
a.table of mean plasma concentration data,
b.table of mean parameters including geometric means(eg from LS means),
c.table containing the individual subject test to reference ratios for Cmax, Tmax, AUC(0-t), AUC(0-inf)
d.table listing the AUC(0-t)/AUC(0-inf) ratio for each subject

4.The firm did not give the name of the person responsible for conducting the analytical assays for the post-prandial study.

5.The firm conducted their post-prandial studies on the following dates:

Group I	August 21	August 28	September 4

Group III September 10 September 11 September 25

Therefore the study involved 6 dosing periods. However, the statistical model used by the firm contained only 3 periods. The revised data for the study should be analyzed with the following model in order to account for all periods. The model is:

Y=GRP SEQ SUBJ(GRP*SEQ) PER(GRP) TRT

Recommendation:

The single dose fasting bioequivalence study conducted by Inwood Laboratories on its Isosorbide Dinitrate Extended release tablets, lot # 94020A,comparing it to Wyeth-Ayerst's Isordil Tembids, 40 mg sustained release tablet, lot 94020A has been found to be incomplete by the Division of Bioequivalence. The single dose post-prandial study conducted by Inwood Laboratories on its Isosorbide Dinitrate Extended release tablets, lot 96064E, comparing it to Wyeth-Ayerst's Isordil Tembids 40 mg sustained release tablets, lot # 9960528 has also been found to be incomplete by the Division of Bioequivalence.

2.The <u>in vitro</u> dissolution testing conducted by Inwood Laboratories on its 40 mg strength Isosorbide dinitrate(lot # 94020A), and on its 40 mg strength Isosorbide dinitrate (lot #96064E)is acceptable.

3.The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of simulated gastric fluid followed by 900 ml of simulated intestinal fluid at 37 C using USP apparatus II paddle at 50 rpm. The test product should meet the following specifications:(Proposed by Division of Bioequivalence in the review of the fasting study April 14, 1995)

Hour 1
Hour 3
Hour 6
Hour 12

Andre J. Jackson
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG Date: 2/9/98

Concur: Date: 2/13/98

Dale P. Conner, Pharm.D
Director,
Division of Bioequivalence

Dissolution Table 1. In Vitro Dissolution Testing

Drug (Generic Name):Isosorbide Dinitrate

Dose Strength:40 mg

ANDA No.:40-009

Firm:Inwood

Submission Date:September 11, 1997

File Name:40009SD.997

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 50

No. Units Tested: 12

Medium: Simulated gastric fluid 1 hr

Simulated intestinal fluid 1-12 hrs

Specifications: Proposed by Division of Bioequivalence

Reference Drug: Isordil

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 94020A Strength(mg) 40			Reference Product Lot # 9940553 Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
1	14		7	14		6
3	38		6	26		6
6	66		7	38		6
12	102		3	51		5

Sampling Times (Hours)	Test Product Lot # 96064E Strength(mg) 40			Reference Product Lot # 9940553 Strength(mg) 40		
	Mean %	Range	%CV	Mean %	Range	%CV
1	14		10	14		6
3	37		10	26		6
6	67		11	38		6
12	99	88-1	5	51	48-5	5

. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 88125D(multiple dose study) Strength(mg) 40			Reference Product Lot # 1880126 Strength(mg) 40 Data not available		
	Mean %	Range	%CV	Mean %	Range	%CV
1	14		8			
3	34		6			
6	56		8			
12	83		4			