CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-009

CORRESPONDENCE

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-009 APPLICANT: Inwood Laboratories

DRUG PRODUCT: Isosorbide Dinitrate 40 mg SR Tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

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	

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues.

Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

Inwood Laboratories
INCORPORATED

909 Third Avenue • New York, NY 10022-4731 • (212) 421-7850

November 2, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA #40-009/Minor Amendment – Chemistry, Manufacturing and Controls**
Product: **Isosorbide Dinitrate Extended-release Tablets USP, 40mg (Peach)**

Dear Mr. Sporn:

We are amending our ANDA #40-009 for the above-referenced drug product to withdraw the following company as a source of the drug material

Wilmington, DE

We have been informed by Zeneca that they can no longer supply the drug material SDM-40 to us.

Sincerely,

INWOOD LABORATORIES, INC.
(Subsidiary of Forest Laboratories, Inc.)

Foma Rashkovsky
Associate Director of Regulatory Affairs

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-009 APPLICANT: Inwood Laboratories

DRUG PRODUCT: Isosorbide Dinitrate 40 mg SR Tablet

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Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues.

Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

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

Inwood Laboratories
INCORPORATED

909 Third Avenue • New York, NY 10022-4731 • (212) 421-7850

June 26, 1998

AMENDMENT
N /AM

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-650
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **ANDA #40-009/Bioequivalency Amendment**
Product: **Isosorbide Dinitrate Extended-release Tablets USP, 40mg (Peach)**

Dear Dr. Conner:

In response to your faxed communication dated February 17, 1998, we address your comments as follows:

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 [redacted] bottles (100 count) stored at 25-30°C/ambient RH 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

Comment #2. You have 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 you 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.

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-96-01-000).

Exhibit 1 shows tables from the original report of the 2-way crossover fasting study (TR/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 (R1) or two (R2) re-assays were done. A second reassay 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 C_{max}, AUC_{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-2-Mononitrate and Isosorbide Dinitrate is included in Exhibit 3.

In-text Table I summarizes the 90% confidence intervals for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the 2-way crossover fasting study (TR/1700/0004). The column "Original Concentrations" presents the 90% confidence intervals for the pharmacokinetic parameters C_{max}, AUC_{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 I 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 I. 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**	**Reassayed Concentrations**
5-ISMN		
C_{max} (ng/mL)	94 - 103	94 - 103
AUC_{0-t} (ng•hr/mL)	103 - 108	103 - 108
$AUC_{0-\infty}$ (ng•hr/mL)	104 - 109	104 - 109
2-ISMN		
C_{max} (ng/mL)	86 - 97	87 - 96
AUC_{0-t} (ng•hr/mL)	103 - 110	103 - 110
$AUC_{0-\infty}$ (ng•hr/mL)	103 - 110	103 - 109

Table I. continued.

ISDN		
C_{max} (ng/mL)	57 - 69	57 - 69
AUC_{0-t} (ng•hr/mL)	94 - 111	93 - 110
$AUC_{0-\infty}$ (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-96-01-000) as provided by nc. 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 R1 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 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 C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and

T_{max}. Tables 25 to 33 list the individual and mean concentrations of Isosorbide-5-Mononitrate, 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 inestimable 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 II summarizes the 90% confidence intervals for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ 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 C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, 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 re-assayed 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 II, 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 II. Comparison of PK Data based on Original and Reassay Concentration Values for the 3-Way Crossover Food Study (ISD-PKA-96-01-000).

	90% confidence intervals, based on log-transformed data	
PK Parameter	**Original Concentrations**	**Reassayed Concentrations**
	IS-5-MN	
C_{max} (ng/mL)	97 - 110	97 - 110
AUC_{0-t} (ng•hr/mL)	97 - 103	97 - 103
$AUC_{0-\infty}$ (ng•hr/mL)	96 - 103	97 - 103
	IS-2-MN	
C_{max} (ng/mL)	94 - 109	95 - 110
AUC_{0-t} (ng•hr/mL)	98 - 105	99 - 106
$AUC_{0-\infty}$ (ng•hr/mL)	98 - 105	99 - 106
	ISDN	
C_{max} (ng/mL)	85 - 114	86 - 114
AUC_{0-t} (ng•hr/mL)	100 - 118	100 - 115
$AUC_{0-\infty}$ (ng•hr/mL)	82 - 97	100 - 115*

* In the original report this 90% confidence interval was given which is based on AUC_{0-t} values instead of $AUC_{0-\infty}$ 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.

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 Isosorbide-2-Mononitrate for Runs 12, 19, 20, 27 and 28. In these cases the chromatograms with the interferences are provided.

Comment #4. You should submit the following tables on a diskette in a WordPerfect 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 (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.

Response:

Tables for (a) mean plasma concentration data, (b) C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$, (c) mean pharmacokinetic parameters, and (d) the ratio of AUC_{0-t} to $AUC_{0-\infty}$ 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.

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 Also included in Exhibit 10 is the curriculum vitae of

Comment #6. You conducted your 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*

Response:

The suggested statistical model was used for the analysis of the 3-way crossover food study (ISD-PKA-96-01-000). 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 C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ 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 1 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 re-assayed 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 Isordil® Tembids® ISDN tablets under fed conditions when administered as a single dose.

The WinNonlin Outputs for the analysis of both studies, the 2-way crossover fasting study (TR/1700/0004) and the 3-way crossover food study (ISD-PKA-96-01-000), are provided as supportive data in Addendum 1 and Addendum 2.

We are also enclosing a copy of your faxed letter of 2/17/98, as you requested.

We trust that the information given herein is satisfactory for the approval of this Application.

Sincerely,

INWOOD LABORATORIES, INC.
(A Subsidiary of Forest Laboratories, Inc.)

Foma Rashkovsky
Associate Director, Regulatory Affairs

Inwood Laboratories
INCORPORATED

909 Third Avenue • New York, NY 10022-4731 • (212) 421-7850

October 14, 1998

Ms. Lizzie Sanchez, Project Manager
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-650
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/FS

Re: **ANDA #40-009/General Correspondence**
Product: **Isosorbide Dinitrate Extended-release Tablets, 40mg (Peach)**

Dear Ms. Sanchez:

In response to your telephone request of October 6, 1998, we are enclosing a replacement diskette which contains data in response to comment #4 of your communication dated February 17, 1998.

The tables were rearranged to address specifically the request in Comment #4, items a, b, c and d. Tables for the 2-way crossover single dose fasting study (TR/1700/0004) may be found in the directory a:\fasted. Tables for the three-way crossover single dose food study (ISD-PKA-96-01-000) may be found in the directory a:\fed. All the table numbers correspond to the tables provided in the original submission with the exception of Tables C1, C2 and C3 which address the specific request in Comment #4 c. All files are in a WordPerfect (Version 6.1) format.

Attached to this transmittal letter, and also included with the diskette, is a "Read me" file that describes the content and organization of this diskette.

A hard copy of the tables with a file name identifying each table, is also provided in Exhibit 1.

Sincerely,
INWOOD LABORATORIES, INC.
(Subsidiary of Forest Laboratories, Inc.)

Foma Rashkovsky
Associate Director, Regulatory Affairs

The tables were rearranged to address specifically the request in Comment #4, items a, b, c and d. Tables for the 2-way crossover single dose fasting study (TR/1700/0004) may be found in the directory a:\fasted. Tables for the 3-way crossover single dose food study (ISD-PKA-96-01-000) may be found in the directory a:\fed. All the table numbers correspond to the tables provided in the original submission with the exception of Tables C1, C2 and C3 which address the specific request in Comment #4 c. All files are in a WordPerfect (Version 6.1) format.

A hard copy of all the tables is also provided in Exhibit 1.

STUDY TR/1700/0004

Comment #4 a: Table of mean plasma concentration data

Response: The tables with the mean plasma data, including standard deviation, %CV, minimum and maximum concentrations, at each time point for the analytes IS-5-MN, IS-2-MN and ISDN are arranged as follows:

A:\fasted\mean\is_5_mn.wpd	contains Tables 1 and 2 with the average concentrations for each time point for the analyte IS-5-MN after administration of the Inwood and the Wyeth ISDN formulations under fasted conditions, respectively.
A:\fasted\mean\is_2_mn.wpd	contains Tables 3 and 4 with the average concentrations for each time point for the analyte IS-2-MN after administration of the Inwood and the Wyeth ISDN formulations under fasted conditions, respectively.
A:\fasted\mean\isdn.wpd	contains Tables 5 and 6 with the average concentrations for each time point for the analyte ISDN after administration of the Inwood and the Wyeth ISDN formulations under fasted conditions, respectively.

Comment #4b: Table of mean parameters including geometric mean (eg from LS means)

Response: The tables with the mean pharmacokinetic parameters including geometric means for the analytes IS-5-MN, IS-2-MN and ISDN are arranged as follows:

A:\fasted\param\is_5_mn.wpd	contains Table 12 with a summary of the mean pharmacokinetic parameters (arithmetic and

geometric) for the analyte IS-5-MN.

A:\fasted\param\is_2_mn.wpd — contains Table 18 with a summary of the mean pharmacokinetic parameters (arithmetic and geometric) for the analyte IS-2-MN.

A:\fasted\param\isdn.wpd — contains Table 24 with a summary of the mean pharmacokinetic parameters (arithmetic and geometric) for the analyte ISDN.

Comment #4c: Table containing the individual subject test to reference ratios for Cmax, Tmax AUC(0-t), AUC(0-inf)

Response: The tables with the individual and mean subject test to reference ratios for C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are arranged as follows:

A:\fasted\indratio\is_5_mn.wpd — contains Tables 7, 8, 9 and 11 with the individual and mean values and subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-5-MN.

A:\fasted\indratio\is_2_mn.wpd — contains Tables 13, 14, 15 and 17 with the individual and mean values and subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-2-MN.

A:\fasted\indratio\isdn.wpd — contains Tables 19, 20, 21 and 23 with the individual and mean values and subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte ISDN.

In addition the following tables were provided:

A:\fasted\indratio\is_5_mna.wpd — contains Table C1 with the individual and mean subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-5-MN.

A:\fasted\indratio\is_2_mna.wpd — contains Table C2 with the individual and mean subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-2-

MN.

A:\fasted\indratio\isdna.wpd — contains Table C3 with the individual and mean subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte ISDN.

Comment #4d: Table listing the AUC(0-t)/AUC(0-inf) ratio for each subject

Response: The tables containing the $AUC_{0-t}/AUC_{0-\infty}$ ratios are arranged as follows:

A:\fasted\aucratio\is_5_mn.wpd — contains Table 10 with the individual and mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for the analyte IS-5-MN.

A:\fasted\aucratio\is_2_mn.wpd — contains Table 16 with the individual and mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for the analyte IS-2-MN.

A:fasted\aucratio\isdn.wpd — contains Table 22 with the individual and mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for the analyte ISDN.

Study ISD-PKA-96-01-000

Comment #4 a: Table of mean plasma concentration data

Response: The tables with the mean plasma data, including standard deviation, %CV, minimum and maximum concentrations, at each time point for the analytes IS-5-MN, IS-2-MN and ISDN are arranged as follows:

A:\fed\mean\is_5_mn.wpd	contains Tables 25, 26 and 27 with the average concentrations for each time point for the analyte IS-5-MN after administration of the Inwood ISDN formulation under fasted and fed conditions and the Wyeth ISDN formulation under fed conditions, respectively.
A:\fed\mean\is_2_mn.wpd	contains Tables 28, 29 and 30 with the average concentrations for each time point for the analyte IS-2-MN after administration of the Inwood ISDN formulation under fasted and fed conditions and the Wyeth ISDN formulation under fed conditions, respectively.
A:\fed\mean\isdn.wpd	contains Tables 31, 32 and 33 with the average concentrations for each time point for the analyte ISDN after administration of the Inwood ISDN formulation under fasted and fed conditions and the Wyeth ISDN formulation under fed conditions, respectively.

Comment #4b: Table of mean parameters including geometric mean (eg from LS means)

Response: The tables with the mean pharmacokinetic parameters including geometric means for the analytes IS-5-MN, IS-2-MN and ISDN are arranged as follows:

A:\fed\param\is_5_mn.wpd	contains Table 39 with a summary of the mean pharmacokinetic (arithmetic and geometric) parameters for the analyte IS-5-MN.
A:\fed\param\is_2_mn.wpd	contains Table 45 with a summary of the mean pharmacokinetic (arithmetic and geometric) parameters for the analyte IS-2-MN.

A:\fed\param\isdn.wpd — contains Table 51 with a summary of the mean pharmacokinetic (arithmetic and geometric) parameters for the analyte ISDN.

Comment #4c: Table containing the individual subject test to reference ratios for Cmax, Tmax AUC(0-t), AUC(0-inf)

Response: The tables with the individual and mean subject test to reference ratios for C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are arranged as follows:

A:\fed\indratio\is_5_mn.wpd — contains Tables 34, 35, 36 and 38 with the individual and mean values and subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-5-MN.

A:\fed\indratio\is_2_mn.wpd — contains Tables 40, 41, 42 and 44 with the individual and mean values and subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-2-MN.

A:\fed\indratio\isdn.wpd — contains Tables 46, 47, 48 and 50 with the individual and mean values and subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte ISDN.

In addition the following tables were provided:

A:\fed\indratio\is_5_mna.wpd — contains Table C1 with the individual and mean subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-5-MN.

A:\fed\indratio\is_2_mna.wpd — contains Table C2 with the individual and mean subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte IS-2-MN.

A:\fed\indratio\isdna.wpd — contains Table C3 with the individual and mean subject test to reference ratios for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, respectively, for the analyte ISDN.

Comment #4d: Table listing the AUC(0-t)/AUC(0-inf) ratio for each subject

Response: The tables containing the $AUC_{0-t}/AUC_{0-\infty}$ ratios for each subject are arranged as follows:

A:\fed\aucratio\is_5_mn.wpd	contains Table 37 with the individual and mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for the analyte IS-5-MN.
A:\fed\aucratio\is_2_mn.wpd	contains Table 43 with the individual and mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for the analyte IS-2-MN.
A:\fed\aucratio\isdn.wpd	contains Table 49 with the individual and mean $AUC_{0-t}/AUC_{0-\infty}$ ratios for the analyte ISDN.

FEB 17 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40009 APPLICANT: Inwood Laboratories

DRUG PRODUCT: Isosorbide Dinitrate
40 mg SR Tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your submitted information on manufacturing is acceptable however, the dissolution data for the 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 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.

2. You have 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 you 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.

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.

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(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

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

6.You conducted your 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

Sincerely yours,

Dale P. Conner

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

BIOEQUIVALENCY DEFICIENCIES

ANDA: 40009 APPLICANT: Inwwod Laboratories

DRUG PRODUCT: Isosorbide Dinitrate
40 mg SR Tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your submitted information on manufacturing is acceptable however, the dissolution data for the 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 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.

2. You have 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 you 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.

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.

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(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

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

6.You conducted your 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

Sincerely yours,

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

ATTACHMENT E

Table 4

ISDN in Human Plasma
Study No. WARS-6088V

Assayed Control Concentrations (ng/ml) and Statistics

Standard Set	Low Control				Medium Control				High Control			
	Assay 1	% Diff	Assay 2	% Diff	Assay 1	% Diff	Assay 2	% Diff	Assay 1	% Diff	Assay 2	% Diff
E1[a]	3.49	-12.8	3.93	-1.8	14.6	-2.7	14.6	-2.7	47.9	-4.2	48.0	-4.0
	3.82	-4.5	3.99	-0.2	15.0	0.0	14.8	-1.3	49.3	-1.4	49.5	-1.0
Mean		3.81				14.8				48.7		
Std. Dev.		0.223				0.19				0.84		
C.V.(%)*		5.9				1.3				1.7		
Theory		4.00				15.0				50.0		
% Diff.**		-4.8				-1.3				-2.6		
Acceptable Control Range+		3.40 - 4.60				12.7 - 17.3				42.5 -57.5		

a Analyzed in Study No. WARS-6037A.

* Values used in the calculation of the C.V. are not truncated.
** Percent difference from theoretical concentration.
\+ Acceptable control range is determined based on ± 20% from theoretical value for the low control range; ± 15% from theoretical values for medium and high control ranges. Used to evaluate daily set acceptability.

ATTACHMENT E

Table 5

2-ISMN in Human Plasma
Study No. WARS-6088V

Assayed Control Concentrations (ng/ml) and Statistics

Standard Set	Low Control				Medium Control				High Control			
	Assay 1	% Diff	Assay 2	% Diff	Assay 1	% Diff	Assay 2	% Diff	Assay 1	% Diff	Assay 2	% Diff
E1[a]	3.76	-6.0	4.06	1.5	16.8	12.0	16.6	10.7	50.1	0.2	51.2	2.4
	4.78	19.5	4.58	14.5	16.7	11.3	16.2	8.0	50.7	1.4	51.5	3.0
Mean		4.30				16.6				50.9		
Std. Dev.		0.468				0.26				0.61		
C.V.(%)*		10.9				1.6				1.2		
Theory		4.00				15.0				50.0		
% Diff.**		7.5				10.7				1.8		
Acceptable Control Range+		3.40 - 4.60				12.7 - 17.3				42.5 -57.5		

a Analyzed in Study No. WARS-6037A.

* Values used in the calculation of the C.V. are not truncated.

** Percent difference from theoretical concentration.

\+ Acceptable control range is determined based on ± 20% from theoretical value for the low control range; ± 15% from theoretical values for medium and high control ranges. Used to evaluate daily set acceptability.

ATTACHMENT E

Table 6

5-ISMN in Human Plasma
Study No. WARS-6088V

Assayed Control Concentrations (ng/ml) and Statistics

Standard Set	Low Control				Medium Control				High Control			
	Assay 1	% Diff	Assay 2	% Diff	Assay 1	% Diff	Assay 2	% Diff	Assay 1	% Diff	Assay 2	% Diff
E1[a]	22.3	11.5	21.4	7.0	85.7	14.3	80.6	7.5	291.2	16.5	282.8	13.1
	17.5	-12.5	17.8	-11.0	70.6	-5.9	76.2	1.6	222.4	-11.0	226.8	-9.3
Mean		19.8				78.3				255.8		
Std. Dev.		2.46				6.42				36.23		
C.V.(%)*		12.4				8.2				14.2		
Theory		20.0				75.0				250.0		
% Diff.**		-1.0				4.4				2.3		
Acceptable Control Range+		16.0 - 24.0				63.8 - 86.3				212.5 - 287.5		

a Analyzed in Study No. WARS-6037A.

* Values used in the calculation of the C.V. are not truncated.

** Percent difference from theoretical concentration.

\+ Acceptable control range is determined based on ± 20% from theoretical value for the low control range; ± 15% from theoretical values for medium and high control ranges. Used to evaluate daily set acceptability.

TABLE I: DEMOGRAPHICS OF SUBJECTS WHO COMPLETED THE STUDY

Subject No.	Subject Initials	Age (yr)	Height (cm)	Weight (kg)	Race
		30	172.7	69.9	Black
		33	175.3	75.3	Hispanic
		23	165.1	68.0	Caucasian
		26	167.6	74.8	Hispanic
		33	177.8	92.5	Hispanic
		31	172.7	78.9	Hispanic
		27	172.7	77.1	Hispanic
		30	175.3	65.8	Hispanic
		23	175.3	65.8	Hispanic
		24	177.8	78.9	Black
		26	175.3	70.8	Black
		28	180.3	64.0	Caucasian
		32	172.7	73.5	Hispanic
		20	172.7	61.7	Hispanic
		30	170.2	64.9	Caucasian
		34	162.6	63.5	Caucasian
		32	172.7	80.7	Caucasian
		35	172.7	76.2	Hispanic
		25	175.3	73.5	Hispanic
		27	177.8	78.0	Caucasian
		31	170.2	68.5	Hispanic
		34	180.3	72.6	Caucasian
		32	172.7	67.6	Asian
		28	160.0	60.3	Hispanic
MEAN		**29**	**173**	**72**	
STD. DEV		**5.4**	**13.1**	**8.5**	

TABLE III: TREATMENTS ADMINISTERED

Subject Numbers	Treatment for Period Number		
	I	II	III
	Isosorbide Dinitrate ER Tablets under fed conditions	- (Did not return, replaced by subject 1R)	-
	Isosorbide Dinitrate ER Tablets under fed conditions	- (Did not return, replaced by subject 1R1)	-
	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[4] Tembids[E] under fed conditions
	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[4] Tembids[E] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[4] Tembids[E] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isordil[E] Tembids[E] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[4] Tembids[E] under fed conditions
	Isordil[E] Tembids[E] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions
	Isordil[E] Tembids[E] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[4] Tembids[E] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isosorbide Dinitrate ER Tablets under fed conditions	- (Did not return, replaced by subject 9R)	-
	Isosorbide Dinitrate ER Tablets under fed conditions	- (Did not return, replaced by subjecr 9R1)	-
	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[4] Tembids[E] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions

Subject Numbers	Treatment for Period Number		
	I	II	III
	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[a] Tembids[a] under fed conditions
	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[a] Tembids[a] under fed conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions
	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[a] Tembids[a] under fed conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[a] Tembids[a] under fed conditions
	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions
	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions
	Isosorbide Dinitrate ER Tablets under fed conditions	- (Did not return, replaced by subject 21R)	-
	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions	Isordil[a] Tembids[a] under fed conditions
	Isordil[a] Tembids[a] under fed conditions	- (Did not return, replaced by subject 22R)	-
	Isordil[a] Tembids[a] under fed conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions

Subject Numbers	Treatment for Period Number		
	I	II	III
	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[b] Tembids[c] under fed conditions	Isosorbide Dinitrate ER Tablets under fasting conditions
	Isosorbide Dinitrate ER Tablets under fasting conditions	Isosorbide Dinitrate ER Tablets under fed conditions	Isordil[a] Tembids[c] under fed conditions

Notes:

Subject 1R was replacement for subject 1 and subject 1R1 was replacement for subject 1R.
Subject 9R was replacement for subject 9 and subject 9R1 was replacement for subject 9R.
Subject 21R was replacement for subject 21.
Subject 22R was replacement for subject 22.

VI

Table 9

Adverse Events - Study Period 1

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TABLE 9
ADVERSE EVENTS - STUDY PERIOD 1

Subject No.	Subject Initials	Study Period	Date of Event	Time of Event	Date of Resolution	Time of Resolution	Description of Adverse Event	Severity	Relationship to Study Drug
		1	08/21/96	1300	08/21/96	2022	Headache	Mild	Probable
		1	08/21/96	1100	08/21/96	1959	Headache	Mild	Probable
		1	08/21/96	1100	08/21/96	2003	Headache	Mild	Probable
		1	08/21/96	1400	08/21/96	2005	Headache	Mild	Probable
		1	08/21/96	0915	08/22/96	0800	Headache	Mild	Probable
			08/21/96	1100	08/21/96	1500	Dizziness	Mild	Probable
			08/21/96	1100	08/21/96	1500	Asthenia	Mild	Possible
		1	08/21/96	0930	08/21/96	2009	Headache	Mild	Probable
		1	08/21/96	1315	08/22/96	0800	Headache	Mild	Probable
		1	08/21/96	1300	08/21/96	2013	Headache	Mild	Probable
		1	08/21/96	0955	08/21/96	1005	Dizziness	Moderate	Probable
			08/21/96	0957	08/21/96	0957	Syncope	Moderate	Probable
		1	08/21/96	1100	08/22/96	0450	Headache	Mild	Probable
		1	08/21/96	1100	08/21/96	2023	Headache	Mild	Probable
		1	08/21/96	1100	08/21/96	2025	Headache	Mild	Probable

TABLE 9 (Continued)
ADVERSE EVENTS - STUDY PERIOD 1

Subject No.	Subject Initials	Study Period	Date of Event	Time of Event	Date of Resolution	Time of Resolution	Description of Adverse Event	Severity	Relationship to Study Drug
		1	08/21/96	1012	08/22/96	0530	Headache	Mild	Probable
			08/21/96	1012	08/22/96	0530	Dizziness	Mild	Probable
		1	08/21/96	1100	08/21/96	1630	Headache	Mild	Probable
		1	08/21/96	1025	08/21/96	1728	Headache	Mild	Probable
		1	08/21/96	1100	08/22/96	0453	Headache	Mild	Probable
		1	08/21/96	1250	08/21/96	1510	Headache	Mild	Probable
		1	08/21/96	0930	08/21/96	1518	Headache	Mild	Probable
		1	09/04/96	1215	09/04/96	1330	Headache	Mild	Probable
		1	09/04/96	0830	09/04/96	0930	Vasodilation	Mild	Possible
			09/04/96	0925	09/04/96	1005	Headache	Mild	Probable
			09/04/96	1100	09/04/96	1635	Headache	Mild	Probable
			09/04/96	2000	09/05/96	0027	Headache	Mild	Probable
			09/05/96	0400	09/05/96	0430	Dizziness	Mild	Possible
			09/05/96	0700	09/10/96	0800	Myalgia, Left Chest	Mild	Unlikely

Total number of adverse events = 29
Total number of subjects reporting adverse events = 20

Table 9-A

Adverse Events - Study Period 2

TABLE 9-A
ADVERSE EVENTS - STUDY PERIOD 2

Subject No.	Subject Initials	Study Period	Date of Event	Time of Event	Date of Resolution	Time of Resolution	Description of Adverse Event	Severity	Relationship to Study Drug
		2	08/28/96	0930	08/29/96	0359	Headache	Mild	Probable
			08/28/96	0930	08/29/96	0359	Dizziness	Mild	Possible
			08/28/96	1159	08/29/96	0300	Pain, Right Calf	Mild	None
		2	08/28/96	1250	08/28/96	1613	Headache	Mild	Probable
		2	08/28/96	0938	08/29/96	0003	Headache	Mild	Probable
		2	08/28/96	1241	08/28/96	1557	Headache	Mild	Probable
		2	08/28/96	1036	08/28/96	1700	Headache	Mild	Probable
		2	08/28/96	1000	08/29/96	0009	Headache	Mild	Probable
		2	08/28/96	1000	08/28/96	1500	Headache	Mild	Probable
		2	08/28/96	1210	08/28/96	1300	Headache	Mild	Probable
			08/28/96	1415	08/28/96	1645	Headache	Mild	Probable
		2	08/28/96	0840	08/28/96	0915	Headache	Mild	Probable
			08/28/96	0935	08/28/96	1011	Vasolilation	Mild	Probable
			08/28/96	1100	08/28/96	1645	Headache	Mild	Probable
		2	08/28/96	0945	08/29/96	0023	Headache	Mild	Probable
			08/28/96	1020	08/28/96	1041	Dizziness	Mild	Probable
01[illegible]	MEP	2	08/28/96	1321	08/28/96	1700	Headache	Mild	Probable

TABLE 9-A
ADVERSE EVENTS - STUDY PERIOD 2 (Continued)

Subject No.	Subject Initials	Study Period	Date of Event	Time of Event	Date of Resolution	Time of Resolution	Description of Adverse Event	Severity	Relationship to Study Drug
		2	08/28/96	0935	08/29/96	0027	Headache	Mild	Probable
		2	08/28/96	0910	08/28/96	1600	Headache	Mild	Probable
			08/28/96	0910	08/28/96	1045	Dizziness	Mild	Probable
		2	08/28/96	0958	08/28/96	1700	Headache	Mild	Probable
		2	08/28/96	1350	08/28/96	1645	Headache	Mild	Probable
		2	08/28/96	1425	08/28/96	1700	Headache	Mild	Probable
		2	08/28/96	2123	08/29/96	0100	Dyspepsia	Mild	Unlikely
		2	09/18/96	1405	09/18/96	2008	Headache	Mild	Probable
		2	09/18/96	1301	09/18/96	1309	Dyspnea	Mild	Possible
			09/18/96	1400	09/18/96	1830	Headache	Mild	Probable
022R	RAR	2	09/18/96	1300	09/18/96	2012	Headache	Mild	Probable

Total number of adverse events = 28
Subjects reporting adverse events = 20

Table 9-B

Adverse Events - Study Period 3

TABLE 9-B
ADVERSE EVENTS - STUDY PERIOD 3

Subject No.	Subject Initials	Study Period	Date of Event	Time of Event	Date of Resolution	Time of Resolution	Description of Adverse Event	Severity	Relationship to Study Drug
		3	09/04/96	1335	09/04/96	1640	Headache	Mild	Probable
		3	09/04/96	1130	09/04/96	2022	Headache	Mild	Probable
		3	09/04/96	1230	09/04/96	2023	Headache	Mild	Probable
		3	09/04/96	1230	09/04/96	2026	Headache	Mild	Probable
		3	09/04/96	0830	09/04/96	1010	Dizziness	Mild	Possible
			09/04/96	1400	09/04/96	1700	Headache	Mild	Possible
		3	09/04/96	1000	09/04/96	2025	Headache	Mild	Probable
		3	09/04/96	1113	09/04/96	1418	Headache	Mild	Probable
		3	09/04/96	0921	09/04/96	0951	Headache	Mild	Probable
		3	09/04/96	0930	09/04/96	1955	Headache	Mild	Probable
		3	09/04/96	0912	09/04/96	1002	Dizziness	Mild	Probable
			09/04/96	0945	09/05/96	1400	Headache	Mild	Probable
			09/04/96	1400	09/04/96	1439	Dizziness	Mild	Probable
		3	09/04/96	1015	09/04/96	1431	Headache	Mild	Probable
	MSN	3	09/25/96	1259	09/25/96	1330	Headache	Mild	Probable

otal number of adverse events = 15
ubjects reporting adverse events = 12

VII

TABLE #14

REASSAY VALUES FOR 2-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

ID		Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
4		21	b	26	68.2[i]			68.2
4		21	b	26	65.9[i]			65.9
4		21	b	26	61.2[i]			61.2
4		21	19.1	29	18.5[l]	29	18.3[l]	19.1[s]
4		21	1.33[h]	28	bql[l]	28	bql[l]	bql
4		21	3.07[h]	28	bql[l]	28	bql[l]	bql
4		21	8.22[h]	28	5.20[l]	28	5.03[l]	5.20
4		21	bql	29	bql[l]	29	k	bql[s]
4		21	bql	29	bql[l]	29	bql[l]	bql[s]
3		1	b	25R	73.9[f,i]	29	k	k
3		1	b	25R	71.8[i]			71.8
3		1	b	25R	85.6[i]			85.6
3		1	b	25R	69.4[i]			69.4
4		3	b	25R	64.6[i]			64.6
4		3	b	25R	61.6[i]			61.6
4		4	b, f	25R	k			k
4		4	b	25R	65.1[l]			65.1
3		5	b	25R	55.0[i]			55.0
3		5	34.5	29	31.7[i]	29	31.9[l]	34.5[s]
3	1	5	33.6	29	30.0[l]	29	29.6[l]	33.6[s]
	2	5	31.4	29	29.1[i]	29	27.4[l]	31.4[s]

b Data not used; greater than the highest theoretical standard curve point.
f High internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 1.00 ng/mL.

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TABLE #14 (Continued)

REASSAY VALUES FOR 2-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

Subject	ID Number	Assay 1 Set	Assay 1 Value	Assay 2 Set	Assay 2 Value	Assay 3 Set	Assay 3 Value	Reported Value
	4 '	22	b	26	60.5[l]			60.5
	4)	22	b	26	k			k
	4 ;	22	b	26	64.9[i]			64.9
	4 ;	22	b	26	53.2[i]			53.2
	4)	22	14.2	29	13.0[i]	29	12.9[l]	14.2[s]
	4)	22	bql[h]	28	bql[i]	28	bql[i]	bql
	4 .	22	1.98[h]	28	bql[i]	28	bql[i]	bql
	4 !	22	6.00[h]	28	bql[l]	28	bql[l]	bql
	4)	22	bql	29	bql[i]	29	k	bql[s]
	4)	22	bql	29	bql[i]	29	k	bql[s]
	! !	8	b	25R	63.2[i]			63.2
	!)	8	b	25R	49.4[i]			49.4
	!)	8	58.9[c]	25R	53.5[i,q]			56.2
	!)	8	b	25R	54.0[i]			54.0
	4 L	8	b	25R	54.6[i]			54.6
	4 !	8	b	25R	71.1[i]			71.1
	4)	8	b	25R	38.8[d,l]	29	k	k

b Data not used; greater than the highest theoretical standard curve point.
c Ratio above highest standard ratio.
d Low internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
q Reassayed inadvertently.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 1.00 ng/mL.

TABLE #14 (Continued)

REASSAY VALUES FOR 2-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	[illegible]	9	b	25R	72.1[i]			72.1
	[illegible]	9	b	25R	78.8[i]			78.8
	[illegible]	9	b	25R	57.1[l]			57.1
	[illegible]	10	b	25R	61.1[i]			61.1
	[illegible]	11	42.5[h]	28	44.8[i]	28	k	43.7
	[illegible]	11	56.9[h]	28	59.4[i]	28	k	58.2
	[illegible]	11	b	25R	76.8[i]			76.8
	[illegible]	11	b	25R	64.0[i]			64.0
	[illegible]	12	90.3[i]	25R	75.7[i,q]	25R	k	83.0
	[illegible]	12	b	25R	79.8[i]			79.8
	[illegible]	12	b	25R	73.7[i]			73.7
	[illegible]	12	b	25R	60.8[i]			60.8
	[illegible]	13	b	25R	66.5[i]			66.5
	[illegible]	13	b	25R	67.8[i]			67.8
	[illegible]	13	bql[d]	25R	bql[i]	25R	k	bql

b Data not used; greater than the highest theoretical standard curve point.
d Low internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
q Reassayed inadvertently.
bql = Below quantifiable limit < 1.00 ng/mL.

TABLE #14 (Continued)

REASSAY VALUES FOR 2-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

Subject	ID Number	Assay 1 Set	Assay 1 Value	Assay 2 Set	Assay 2 Value	Assay 3 Set	Assay 3 Value	Reported Value
:	?	14	b	25R	80.0[i]			80.0
:	3	14	b	25R	56.5[i]			56.5
:	3	14	a	26	bql[i]	26	k	bql
:	)	14	b	25R	64.2[i]			64.2
:	.	14	b	25R	73.5[i]			73.5
:	3	14	a	26	bql[i]	26	k	bql
‹	?	14	b	25R	67.8[l]			67.8
‹	3	14	b	25R	64.0[i]			64.0
‹	5	15	b	26	88.3[i]			88.3
‹	5	15	b	26	73.8[i]			73.8
:	?	16R	b	26	64.8[i]			64.8
:	3	16R	b	26	63.7[i]			63.7
:	?	16R	b	26	81.6[i]			81.6
:	3	16R	b	26	72.9[i]			72.9
:	3	16R	3.33[d]	26	bql[i]	26	k	n
‹	?	16R	b	26	72.4[i]			72.4
‹	3	16R	b	26	65.7[i]			65.7

a Data not used due to a laboratory accident.
b Data not used; greater than the highest theoretical standard curve point.
d Low internal standard.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
n No value reported due to values not meeting PPD Pharmaco matching criteria.
bql = Below quantifiable limit < 1.00 ng/mL.

TABLE #14 (Continued)

REASSAY VALUES FOR 2-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

Subject ID	Number	Assay 1 Set	Assay 1 Value	Assay 2 Set	Assay 2 Value	Assay 3 Set	Assay 3 Value	Reported Value
	5	17	b	26	bql[i,p]	28	51.4[i]	51.4
	1	17	bql[e]	26	bql[i]	26	k	bql
	3	17	bql[e]	26	bql[i]	26	k	bql
	1	17	bql[e]	26	65.2[i,p]	28	bql[l]	bql
	7	17	b	26	66.9[i]			66.9
	3	17	b	26	58.7[i]			58.7
	3	17	bql[e]	26	bql[i]	26	k	bql
	1	17	bql[e]	26	bql[i]	26	k	bql
	1	27	43.0[i]	29	39.6[l]			43.0[s]
	2	27	38.2[i]	29	33.3[l]			38.2[s]
	3	27	31.8[i]	29	30.3[l]			31.8[s]
	1	27	26.2[i]	29	25.5[l]			26.2[s]
	5	27	2.53[i]	29	bql[l]			2.53[s]
	5	27	2.58[i]	29	bql[l]	29	bql[l]	2.58[s]
	7	27	bql[i]	29	bql[l]			bql[s]
	2	18	b	26	66.0[i]			66.0
	2	18	b	26	67.7[i]			67.7
	4353	18	b	26	59.5[i]			59.5

b Data not used; greater than the highest theoretical standard curve point.
e Interference peak present.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
p Data not used in reported value due to Patient Number 3575 and 3984 suspected of being switched during assay.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 1.00 ng/mL.

TABLE #14 (Continued)

REASSAY VALUES FOR 2-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

Subject	ID Number	Assay 1 Set	Assay 1 Value	Assay 2 Set	Assay 2 Value	Assay 3 Set	Assay 3 Value	Reported Value
		23	b	26	61.7[i]			61.7
		23	39.9	29	35.6[l]	29	35.1[l]	39.9[s]
		23	25.7	29	24.2[i]	29	25.2[l]	25.7[s]
		23	1.63[h]	28	bql[i]	28	bql[i]	bql
		23	4.30[h]	28	bql[l]	28	bql[l]	bql
		23	14.4[h]	26	13.8[l]	26	14.3[l]	14.3
		23	bql	29	bql[l]	29	k	bql[s]
		23	bql	29	bql[i]	29	bql[l]	bql[s]
		24	b	26	64.3[l]			64.3
		24	33.1	29	31.1[l]	29	30.2[l]	33.1[s]
		24	19.3	29	18.2[i]	29	18.9[l]	19.3[s]
		24	bql[h]	28	bql[l]	28	bql[l]	bql
		24	2.36[h]	28	bql[i]	28	bql[i]	bql
		24	8.07[h]	28	5.09[l]	28	4.99[l]	5.09
		24	bql	29	bql[i]	29	bql[l]	bql[s]
		24	bql	29	bql[i]	29	bql[l]	bql[s]
		19	bql[d]	26	k			k
		19	bql[d]	26	bql[i]	26	k	bql
		19	bql[d]	26	bql[i]	26	k	bql
		20	bql[e]	26	bql[i]	26	k	bql
		20	b	26	55.1[i]			55.1

b Data not ed; greater than the highest theoretical standard rve point.
d Low internal standard.
e Interference peak present.
h Reassayed due to sample value not fitting pharmacokinetic profile.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 1.00 ng/mL.

TABLE #15

REASSAY VALUES FOR 5-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	[illegible]3	21	b	26	319.3[j]			319.3
	[illegible]4	21	201.1	29	171.2[m]	29	165.1[m]	201.1[s]
	[illegible]5	21	55.2[h]	28	42.5[m]	28	45.5[m]	45.5
	[illegible]6	21	86.4[h]	28	70.8[m]	28	74.4[m]	74.4
	[illegible]7	21	130.9[h]	28	122.6[m]	28	124.9[m]	124.9
	[illegible]8	21	35.6	29	28.3[m]	29	k	35.6[s]
	[illegible]9	21	27.7	29	bql[m]	29	bql[m]	27.7[s]
	[illegible]2	1	b	25R	320.7[f,j]	29	k	k
	[illegible]3	1	b	25R	356.2[j]			356.2
	[illegible]0	1	b	25R	350.5[j]			350.5
	[illegible]1	1	b	25R	325.6[j]			325.6
	[illegible]2	3	b	25R	341.6[j]			341.6
	[illegible]2	3	b	25R	359.5[j]			359.5
	[illegible]3	4	287.4[f]	25R	302.8[m]	25R	k	295.1
	[illegible]0	5	166.3	29	149.2[j]	29	138.6[m]	166.3[s]
	[illegible]1	5	177.4	29	143.7[m]	29	140.8[m]	177.4[s]
	[illegible]2	5	172.0	29	164.6[j]	29	145.7[m]	172.0[s]

b Data not used; greater than the highest theoretical standard curve point.
f High internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
j Assayed at partial volume 0.50 mL; elevated bql < 10.0 ng/mL.
k No result possible due to insufficient sample volume for reassay.
m Assayed at partial volume 0.25 mL; elevated bql < 20.0 ng/mL.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 5.00 ng/mL.

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TABLE #15 (Continued)

REASSAY VALUES FOR 5-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	9	22	163.7	29	160.2[j]	29	147.2[m]	163.7[s]
	)	22	46.9[h]	28	46.1[j]	28	45.9[j]	46.1
	L	22	75.9[h]	28	71.7[j]	28	72.0[j]	72.0
	2	22	115.5[h]	28	113.1[j]	28	117.4[j]	115.5
	3	22	30.8	29	24.5[j]	29	k	30.8[s]
	5	22	13.5	29	bql[j]	29	k	13.5[s]
		9	b	25R	352.4[j]			352.4
		11	201.7[h]	28	209.3[j]	28	k	205.5
		11	286.4[h]	28	277.8[j]	28	k	282.1
4		11	b	25R	337.0[j]			337.0
3		12	424.4[j]	25R	355.2[j,q]	25R	k	389.8
3		12	b	25R	288.2[j]			288.2
3		12	b	25R	329.0[j]			329.0
3		12	b	25R	370.5[j]			370.5
4		12	b	25R	346.4[j]			346.4
4		12	b	25R	363.5[j]			363.5
4		13	b	25R	295.2[j]			295.2
4		13	32.1[d]	25R	14.3[j]	25R	k	n

b Data not used; greater than the highest theoretical standard curve point.
d Low internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
j Assayed at partial volume 0.50 mL; elevated bql < 10.0 ng/mL.
k No result possible due to insufficient sample volume for reassay.
m Assayed at partial volume 0.25 mL; elevated bql < 20.0 ng/mL.
n No value reported due to values not meeting PPD Pharmaco matching criteria.
q Reassayed inadvertently.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 5.00 ng/mL.

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TABLE #15 (Continued)

REASSAY VALUES FOR 5-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	[illegible]2	14	b	25R	350.8[j]			350.8
	[illegible]3	14	b	25R	316.7[j]			316.7
	[illegible]3	14	a	26	30.3[j]			30.3
	[illegible]1	14	b	25R	342.7[j]			342.7
	[illegible]2	14	b	25R	342.2[j]			342.2
	[illegible]3	14	a	26	26.9[j]			26.9
	[illegible]3	16R	b	26	348.0[j]			348.0
	[illegible]2	16R	b	26	415.6[j]			415.6
	[illegible]3	16R	b	26	390.9[j]			390.9
	[illegible]3	16R	45.2[d]	26	46.3[j]	26	k	45.8
	[illegible]5	16R	5.18[g]	26	k			k
	[illegible]2	16R	b	26	430.9[j]			430.9
	[illegible]3	16R	b	26	233.3[j]			233.3
	[illegible]1	18	218.6	29	204.4[m]			218.6[s]
	[illegible]2	18	218.9	29	197.5[m]			218.9[s]
	[illegible]3	18	212.9	29	204.8[m]			212.9[s]
	[illegible]4	18	216.1	29	197.5[m]			216.1[s]
	[illegible]5	18	104.4	29	79.4[m]			104.4[s]
	[illegible]5	18	106.7	29	81.4[m]	29	78.2[m]	106.7[s]
	3597	18	67.8	29	53.9[m]			67.8[s]

a Data not used due to a laboratory accident.
b Data not used; greater than the highest theoretical standard curve point.
d Low internal standard.
g Reassayed due to quantifiable pre-dose concentration.
j Assayed at partial volume 0.50 mL; elevated bql < 10.0 ng/mL.
k No result possible due to insufficient sample volume for reassay.
m Assayed at partial volume 0.25 mL; elevated bql < 20.0 ng/mL.
s Reassayed at client's request; original value reported.

TABLE #15 (Continued)

REASSAY VALUES FOR 5-ISMN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	3	23	227.3	29	190.8[m]	29	197.8[m]	227.3[s]
	9	23	211.0	29	196.6[j]	29	193.2[m]	211.0[s]
	0	23	60.6[h]	28	60.8[j]	28	59.7[j]	60.6
	1	23	97.3[h]	28	84.2[m]	28	83.2[m]	84.2
	2	23	162.9[h]	26	157.0[m]	26	153.5[m]	157.0
	3	23	39.8	29	36.2[m]	29	k	39.8[s]
	4	23	17.4	29	15.5[j]	29	bql[m]	17.4[s]
	3	24	b	26	288.4[j]			288.4
	3	24	241.3	29	230.0[m]	29	215.8[m]	241.3[s]
	4	24	189.0	29	176.5[j]	29	170.4[m]	189.0[s]
	5	24	45.1[h]	28	34.0[m]	28	31.6[m]	34.0
	5	24	80.9[h]	28	67.7[j]	28	68.0[j]	68.0
	7	24	126.4[h]	28	108.2[m]	28	105.5[m]	108.2
	3	24	25.7	29	22.5[j]	29	bql[m]	25.7[s]
	9	24	11.7	29	bql[j]	29	bql[m]	11.7[s]
	0	19	bql[d]	26	k			k
	3	19	45.6[d]	26	40.6[j]	26	k	43.1
	3	19	53.3[d]	26	46.5[j]	26	k	49.9

b Data not used; greater than the highest theoretical standard curve point.
d Low internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
j Assayed at partial volume 0.50 mL; elevated bql < 10.0 ng/mL.
k No result possible due to insufficient sample volume for reassay.
m Assayed at partial volume 0.25 mL; elevated bql < 20.0 ng/mL.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 5.00 ng/mL.

TABLE #16

REASSAY VALUES FOR ISDN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	[illegible]	21	bql	29	bql[l]	29	bql[l]	bql[s]
	[illegible]	21	bql[h]	28	bql[l]	28	bql[l]	bql
	[illegible]	21	bql[h]	28	bql[l]	28	bql[l]	bql
	[illegible]	21	bql[h]	28	bql[l]	28	bql[l]	bql
	[illegible]	21	bql	29	bql[l]	29	k	bql[s]
	[illegible]	21	bql	29	bql[l]	29	bql[l]	bql[s]
	[illegible]	4	19.0[f]	25R	k			k
	[illegible]	5	7.18	29	4.65[i]	29	bql[l]	7.18[s]
	[illegible]	5	5.34	29	bql[l]	29	bql[l]	5.34[s]
	[illegible]	5	4.86	29	2.34[i]	29	bql[l]	4.86[s]
	[illegible]	22	bql	29	bql[i]	29	bql[l]	bql[s]
	[illegible]	22	bql[h]	28	bql[i]	28	bql[i]	bql
	[illegible]	22	bql[h]	28	bql[i]	28	bql[i]	bql
	[illegible]	22	bql[h]	28	bql[i]	28	bql[i]	bql
	[illegible]	22	bql	29	bql[i]	29	k	bql[s]
	[illegible]	22	bql	29	bql[i]	29	k	bql[s]

f High internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 1.00 ng/mL.

TABLE #16 (Continued)

REASSAY VALUES FOR ISDN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	5	11	5.32[h]	28	5.55[i]	28	k	5.44
	7	11	13.8[h]	28	14.8[i]	28	k	14.3
	7	12	2.62[e]	28	2.18[i]	28	k	2.40
	0	12	8.89[e]	25R	7.47[i]	25R	k	8.18
	4	13	bql[d]	25R	k			k
	8	14	a	26	bql[i]			bql
	8	14	a	26	bql[i]			bql
	6	16R	bql[e]	26	bql[i]	26	k	bql
	8	16R	bql[d]	26	bql[i]	26	k	bql
	1	18	7.78	29	7.27[l]			7.78[s]
	2	18	5.37	29	7.06[l,e]			5.37[s]
	3	18	4.19	29	6.17[l,e]			4.19[s]
	4	18	4.82	29	5.32[l]			4.82[s]
	5	18	bql	29	bql[l]			bql[s]
	6	18	bql	29	bql[l]			bql[s]
20	0097	18	bql	29	bql[l]			bql[s]

a Data not used due to a laboratory accident.
d Low internal standard.
e Interference peak present.
h Reassayed due to sample value not fitting pharmacokinetic profile.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 1.00 ng/mL.

TABLE #16 (Continued)

REASSAY VALUES FOR ISDN IN HUMAN PLASMA
STUDY ISD-PKA-96-01-000

	ID	Assay 1		Assay 2		Assay 3		Reported
Subject	Number	Set	Value	Set	Value	Set	Value	Value
	3	23	7.91	29	bql[l]	29	bql[l]	7.91[s]
	9	23	3.71	29	bql[i]	29	bql[l]	3.71[s]
	0	23	bql[h]	28	bql[i]	28	bql[i]	bql
	1	23	bql[h]	28	bql[l]	28	bql[l]	bql
	2	23	1.48[h]	26	bql[l]	26	bql[l]	bql
	3	23	bql	29	bql[l]	29	k	bql[s]
	4	23	bql	29	bql[i]	29	bql[l]	bql[s]
	3	24	5.14	29	bql[l]	29	bql[l]	5.14[s]
	4	24	3.39	29	bql[i]	29	bql[l]	3.39[s]
	5	24	bql[h]	28	bql[i]	28	bql[i]	bql
	5	24	bql[h]	28	bql[i]	28	bql[i]	bql
	7	24	bql[h]	28	bql[l]	28	bql[l]	bql
	8	24	bql	29	bql[i]	29	bql[l]	bql[s]
	9	24	bql	29	bql[i]	29	bql[l]	bql[s]
23	4043	19	bql[d]	26	bql[i]	26	k	bql

d Low internal standard.
h Reassayed due to sample value not fitting pharmacokinetic profile.
i Assayed at partial volume 0.50 mL; elevated bql < 2.00 ng/mL.
k No result possible due to insufficient sample volume for reassay.
l Assayed at partial volume 0.25 mL; elevated bql < 4.00 ng/mL.
s Reassayed at client's request; original value reported.
bql = Below quantifiable limit < 1.00 ng/mL.

Inwood Laboratories
INCORPORATED

909 Third Avenue • New York, NY 10022-4731 • (212) 421-7850

April 14, 1995

NEW CORRESP

Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-650
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
APR 17 1995
GENERIC DRUGS

Re: **ANDA #40-009 - Response to FDA letter of March 15, 1994**

Product: **Isosorbide Dinitrate Extended-release Tablets, 40mg**

Dear Sir:

In response to your communication dated March 15, 1994, we are submitting a full scale study report which was conducted to support the Bioequivalence claims for Isosorbide Dinitrate 40mg ER Tablets.

This study, TR/1700/0004, was conducted to evaluate the rate and extent of absorption of a single dose of Inwood Isosorbide Dinitrate ER Tablets, 40mg compared to the reference product, Wyeth-Ayerst Isordil® Tembids® 40mg in a randomized, two way crossover study in twenty-eight normal, healthy, non-smoking male volunteers under fasted conditions.

The study clearly demonstrates that Inwood Isosorbide Dinitrate 40mg ER Tablets is bioequivalent to Wyeth-Ayerst Isordil® Tembids® with respect to IS2MN and IS5MN two major metabolites of the parent drug Isosorbide ditrate, (ISDN) and Total Nitrate following single dose administration. The relative bioavailability and two one sided t procedure on log-transformed C_{max}, AUC o-t and AUC o-∞ for IS2MN, IS5MN and Total Nitrate, and AUC o-t

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APR 17 1995
GENERIC DRUGS

for ISDN are within accepted 80-125% limit. Study TR/1700/0004 is therefore, acceptable for the determination of bioequivalence.

We trust this meets with you approval.

Sincerely,

INWOOD LABORATORIES, INC.
(Subsidiary of Forest Laboratories, Inc.)

Michael M. Rosen, Ph.D.
Director of Regulatory Affairs

MMR:nc

Inwood Laboratories
INCORPORATED

909 Third Avenue • New York, NY 10022-4731 • (212) 421-7850

re 11/6/97

October 31, 1997

ORIG AMENDMENT
N/AB

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

Re: **ANDA #40-009/Response To FDA Request For Information/Bioequivalance**
Product: **Isosorbide Dinitrate Extended-Release Tablets USP, 40 Mg (Peach)**

Dear Mr. Sporn:

On October 23, 1997, we received a telephone call from Ms. Nancy Chamberlin, a CSO from the Bioequivalence division, requesting electronic files for the following bioequivalence studies which we have submitted:

1. "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).

2. "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).

3. "A Three-way Crossover, Single Dose, Bioequivalency Study of Isosorbide Dinitrate ER Tablets, 40 mg in Fasted and Fed Male Volunteers." (Report # TR/ISD-PKA-96-01-000, submitted 9/2/97).

Ms. Chamberlin asked us to submit individual concentration data and summary tables for the above mentioned studies (in ASCII format for concentration data and in text-WP format for summary tables). The moieties to be reported upon are ISDN and its two metabolites, 5-mononitrate and 2-mononitrate.

RECEIVED

Enclosed is a 3.5" diskette containing the above information. A hard copy of the readme file is also enclosed.

NOV 5 1997

GENERIC DRUGS

If you need any further information, please let me know.

Sincerely,

INWOOD LABORATORIES, INC.
(A Subsidiary of Forest Laboratories, Inc.)

Foma Rashkovsky
Associate Director, Regulatory Affairs

FR/kb

AM noted
① To chemistry reviewer, then
② To labeling
NA
9/19/97

Inwood Laboratories
INCORPORATED

909 Third Avenue • New York, NY 10022-4731 • (212) 421-7850

September 11, 1997

NDA ORIG AMENDMENT

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food and Drug Administration
Metro Park North II, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA #40-009/Minor Amendment-Chemistry, Manufacturing and Controls/Labeling**
Product: **Isosorbide Dinitrate Extended-release Tablets USP, 40mg (Peach)**

Dear Mr. Sporn:

We wish to respond to your letter of April 4, 1996, concerning our Amendment submitted August 18, 1995 to our ANDA #40-009 for Isosorbide Dinitrate Extended-release Tablets USP 40mg (Peach). We address your comments as follows:

Comment:

A. *Chemistry Deficiencies*

1. *Your composition statement [illegible]*

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

9/11/97

Response:

Attachment 3 is a request for categorical exclusion from Environmental Impact Considerations.

Attachment 4 is a certification that the manufacturing of the drug product will be in compliance with applicable federal, state and local environmental laws.

Comment:

B. Labeling Deficiencies

I. INSERT

a. GENERAL COMMENT

The labeling for the reference listed drug, Isordil Tembids (Isosorbide Dinitrate) Controlled-release Tablets and Capsules has been changed. Please revise your insert labeling to conform with the most recently approved insert labeling (Approved 9-6-95, Revised 4-19-95). A copy has been enclosed with this correspondence.

DESCRIPTION - Last paragraph

i. Each Isosorbide Dinitrate Extended-release tablet, for oral administration, contains 40 mg of Isosorbide Dinitrate, in a matrix that causes the active drug to be released over a sustained period. In addition, each tablet also contains the following inactive ingredients:...

ii. Revise the listing of inactive ingredients to read:

...anhydrous lactose,...

c. HOW SUPPLIED

i. Include "USP" with the established name in this section.

ii. *We note that you have described your tablet as "Imprinted" yet there is no mention of an imprinting ink in your submission. Please Comment.*

Please revise your insert labeling, as instructed above, and submit draft insert labeling.

Response:

The package insert (draft, rev. 7/97) has been modified according to your recommendations. Additional information from a recently conducted bioequivalence study (study report submitted under separate cover) has been included (pharmacokinetics, paragraph #4). Enclosed for your review are four (4) copies of the draft insert (Attachment 5).

Comment:

We note that you have submitted alternate analytical methods to be used in the testing of drug substance and/or drug product. Please be advised that approval to use an analytical procedure that differs from that in the USP does not release your firm from any obligations to comply with the methods and procedures in the USP. You should be aware that USP procedures remain the regulatory method, and results obtained thereof will rule in the event of a dispute.

Response:

We acknowledge that approval to use an alternate analytical method does not release us from any obligations to comply with the methods and procedures in the USP.

Please note that we have updated Analytical Method (Attachment 6).
The following changes were made:

II. A section in related substances was changed to read "
of each of the following solutions:

The changes were made because not enough with the original description.

III. Dissolution Changes:

A.

B. The following entries were removed as they are not applicable:

e

IV. Column preparation and equilibration and nutdown were updated to reflect current laboratory practices.

V. Dissolution parameters at 6 hours have been changed from
reflect current stability data.

As you requested, a response to the bioequivalency deficiencies has been submitted to the Division prior to the present submission.

We trust that the information given herein is sufficient for the approval of this Application.

Sincerely,

INWOOD LABORATORIES, INC.
(Subsidiary of Forest Laboratories, Inc.)

Foma Rashkovsky
Associate Director, Regulatory Affairs

OWS\C:\DATA\BURTON\NEWFDABA.WPD