

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75041

BIOEQUIVALENCE REVIEW(S)

3-1
JUN 15 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-041

APPLICANT: Elan Pharmaceutical
Research Corp.

DRUG PRODUCT: Isosorbide Mononitrate ER Tablets, 60 mg

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

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The dissolution testing data should be conducted on a validation batch. The dissolution data should include type and volume of the medium, temperature, apparatus type and rotation speed, the assay method that has been used, and the date the testing was performed.

The comparative dissolution profiles for the test and reference products (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis. Comparative dissolution data for both the test and reference drug products, should be performed simultaneously. In addition, the lot number, lot size (for the test product only), and the manufacturing date for the test product and expiration date for the reference product should be included.

Method of Dissolution testing as specified in the Agency Guidance "Oral Extended (Controlled) Release: Dosage Forms, In Vitro Bioequivalence and In Vitro Dissolution Testing" dated September 09, 1993.

General conditions are as follows:

Apparatus:	USP 23 Apparatus 2 (paddle)
RPM:	50 and 75 rpm
Medium:	Buffer media with pH* ranges: 1-1.5, 4-4.5, 6-6.5, 7-7.5 and water.
Volume:	900 mL
Sampling Times:	1, 2, and 4 hours, and every two hours until 80% of the drug is released

Tolerance (Q): As established
Analytical: As per USP 23, if available, or other
validated method

* Buffered media are to be prepared as per USP 23, pp 2049-2050.

Please note: for a scored tablet; dissolution test for half-tablet testing is required. Twelve (12) tablets should be broken, and each half of each tablet should be tested so that 12 separate units are tested for test and reference product. Testing should not be conducted by breaking 6 tablets into 12 halves and testing the 12 halves, i.e., each half tested should come from a separate tablet.

Sincerely yours,

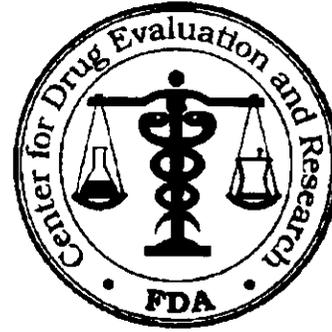
/S/

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

BIOEQUIVALENCY AMENDMENT

ANDA 75-041

JUN 15 1998



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Elan Pharmaceutical Research Corp. PHONE: 770-534-8239
ATTN: Roger Wayne Wiley FAX: 770-534-8247

FROM: Nancy Chamberlin PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on 2-20-98 and 5-6-98, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Isosorbide Mononitrate 60 mg extended release tablets.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed.** Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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DEC 16 1997

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-041

APPLICANT: Elan Corporation

DRUG PRODUCT: Isosorbide Mononitrate Extended Release Tablets,
60 mg

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

1. Dissolution Testing

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested *in vivo*.

You conducted dissolution on only the test product in distilled water as the medium. You did not provide comparative dissolution with the reference product and individual dissolution data, mean, CV% and range for the test and the reference product.

You provided comparative dissolution data of test and reference product in buffered media of pH 1.2 - 7.2 using U.S.P. apparatus II, 900 ml of media and rotation speed of rpm. Dissolution tests conducted with rpm are not acceptable. Apparatus 2 with rotation speed of either 50 or 75 rpm should be used.

Method of Dissolution testing as specified in Guidance for In-Vitro Dissolution testing for extended release formulation is shown below.

General conditions are as follows:

Apparatus:	USP 23 Apparatus 2 (paddle)
RPM:	50 or 75 rpm
Medium:	aqueous buffered media of various pH*
Volume:	900 mL
Sampling Times:	1, 2, and 4 hours, and every two hours until 80% of the drug is released
Tolerance (Q):	As established
Analytical:	As per USP 23, if available, or other validated method

* Dissolution should be conducted in buffered media with pH of 1.2, 4.2, 6.2 and 7.2, buffered media are to be prepared as per USP23, pp2049 - 2050.

Isosorbide Mononitrate
60 mg Extended-Release Tablets
ANDA #75-041
Reviewer: Z.Z. Wahba
File #75041a.298

Elan Pharmaceutical
Gainesville, GA
Submission Date:
February 20, 1998
May 06, 1998

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm has previously submitted three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple dose) comparing its test product Isosorbide Mononitrate Extended-Release (ER) Tablets, 60 mg to the reference listed product, Schering's Imdur® Extended Release Tablets, 60 mg.
2. The submission was reviewed and was found incomplete by the Division of Bioequivalence (the submission dated Dec. 31, 1996, ANDA #75-041, reviewed by A. Patel) due to deficiency comments.
3. In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

COMMENT #1

The firm was asked to submit comparative dissolution testing data conducted on 12 dosage units of the test product versus 12 units of the reference product. The dissolution testing should be done on tablets from the same lot number as that used in the in vivo bioequivalence studies.

RESPONSE TO COMMENT #1

The firm submitted comparative dissolution data (on February 20, 1998) on the bio-lot that expired September 1997.

The firm's response to comment #1 is unacceptable.

COMMENT #2

The graphs of dissolution profiles show an incorrect x-axis scale (no break in the axis) and instead of a 22 hour data point, a 24 hour data point is plotted. This needs clarification.

RESPONSE TO COMMENT #2

The firm provided the corrected graphs. However, the graphs were related to the dissolution data from the expired bio-lot.

No action is needed on comment #2

DEFICIENCY:

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The dissolution testing data should be conducted on a **validation batch**. The dissolution data should include type and volume of the medium, temperature, apparatus type and rotation speed, the assay method that has been used, and the date the testing was performed.

The comparative dissolution profiles for the test and reference products (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis. Comparative dissolution data for both the test and reference drug products, should be performed simultaneously. In addition, the lot number, lot size (for the test product only), and the manufacturing date for the test product and expiration date for the reference product should be included.

Method of Dissolution testing as specified in the Agency Guidance "Oral Extended (Controlled) Release: Dosage Forms, *In Vitro* Bioequivalence and *In Vitro* Dissolution Testing" dated September 09, 1993.

General conditions are as follows:

Apparatus:	USP 23 Apparatus 2 (paddle)
RPM:	50 and 75 rpm

Medium: Buffer media with pH* ranges: 1-1.5, 4-4.5, 6-6.5, 7-7.5 and water.
Volume: 900 mL
Sampling Times: 1, 2, and 4 hours, and every two hours until 80% of the drug is released
Tolerance (Q): As established
Analytical: As per USP 23, if available, or other validated method

* Buffered media are to be prepared as per USP 23, pp 2049-2050.

Please note: for a scored tablet; dissolution test for half-tablet testing is required. Twelve (12) tablets should be broken, and each half of each tablet should be tested so that 12 separate units are tested for test and reference product. Testing should not be conducted by breaking 6 tablets into 12 halves and testing the 12 halves, i.e., each half tested should come from a separate tablet.

RECOMMENDATIONS

The bioequivalence study application submitted by Elan Pharmaceutical Research Corp. for its Isosorbide Mononitrate ER Tablets, 60 mg, is incomplete.

The firm should be informed of the recommendation and deficiency.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

/S/

Concur: _____

/S/

: 6/10/98

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

BIOEQUIVALENCY DEFICIENCIES

ANDA: #75-041

APPLICANT: Elan Pharmaceutical
Research Corp.

DRUG PRODUCT: Isosorbide Mononitrate ER Tablets, 60 mg

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

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The dissolution testing data should be conducted on a validation batch. The dissolution data should include type and volume of the medium, temperature, apparatus type and rotation speed, the assay method that has been used, and the date the testing was performed.

The comparative dissolution profiles for the test and reference products (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis. Comparative dissolution data for both the test and reference drug products, should be performed simultaneously. In addition, the lot number, lot size (for the test product only), and the manufacturing date for the test product and expiration date for the reference product should be included.

Method of Dissolution testing as specified in the Agency Guidance "Oral Extended (Controlled) Release: Dosage Forms, In Vitro Bioequivalence and In Vitro Dissolution Testing" dated September 09, 1993.

General conditions are as follows:

Apparatus:	USP 23 Apparatus 2 (paddle)
RPM:	50 and 75 rpm
Medium:	Buffer media with pH* ranges: 1-1.5, 4-4.5, 6-6.5, 7-7.5 and water .
Volume:	900 mL
Sampling Times:	1, 2, and 4 hours, and every two hours until 80% of the drug is released

Tolerance (Q): As established.
Analytical: As per USP 23, if available, or other
validated method

* Buffered media are to be prepared as per USP 23, pp 2049-2050.

Please note: for a scored tablet; dissolution test for half-tablet testing is required. Twelve (12) tablets should be broken, and each half of each tablet should be tested so that 12 separate units are tested for test and reference product. Testing should not be conducted by breaking 6 tablets into 12 halves and testing the 12 halves, i.e., each half tested should come from a separate tablet.

Sincerely yours,

/S/

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

CC:

File

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BIOEQUIVALENCY - ACCEPTABLE

Submission date: 2-20-97

1. **STUDY AMENDMENT** dated February 20, 1998 Strengths: 600 mg
Outcome: IC
2. **STUDY AMENDMENT** dated May 06, 1998 Strengths: 600 mg
Outcome: IC

OUTCOME DECISIONS: IC - Incomplete IC - Incomplete

WINBIO COMMENTS: Incomplete Biostudy

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #75-041. APPLICANT: Elan Pharmaceutical Corp.

DRUG PRODUCT: Isosorbide Mononitrate ER Tablets, 60 mg

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 1000 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data, the following tentative specifications are recommended for Isosorbide Mononitrate ER Tablet, 60 mg:

0.5	hour	NLT	and	NMT
2.0	hour	NLT	and	NMT
4.0	hours	NLT	and	NMT
8.0	hours	NLT	;	and NMT
12	hours	NLT	;	

Important note:

You are required to submit dissolution data from your first three production batches using the above-mentioned dissolution method. The dissolution testing should be done on whole tablets as well as half-tablets. The dissolution profile which you submit should be accompanied by dissolution data from a current batch of the reference listed drug.

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

CC: ANDA #75-041

Endorsements:

X:\NEW\FIRMSAN\ELAN\ltrs&rev\75041a2.m98

BIOEQUIVALENCY - ACCEPTABLE

1. **STUDY AMENDMENT** dated July 01, 1998 Strengths: 60 mg
Outcome: AC
2. **STUDY AMENDMENT** dated July 15, 1998 Strengths: 60 mg
Outcome: AC

OUTCOME DECISIONS: **AC** - Acceptable
WINBIO COMMENTS: Acceptable Biostudy



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

July 24, 1998

NEW CORRESP

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER, Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

BIOAVAILABILITY
NC/h.copv

RE: MINOR TELEPHONE AMENDMENT
ANDA 75-041: Isosorbide Mononitrate Extended-release Tablets, 60 mg
Hard Copy of July 15, 1998 Telefaxed Response

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application for Isosorbide Mononitrate Extended-release Tablets, 60 mg (ANDA 75-041) received by the FDA Office of Generic Drugs on December 31, 1996.

Attached please find the telefax submitted on July 15, 1998 in regards to dissolution specifications for the stability summary report submitted in the July 1 submission to the Division of Bioequivalence.

Please feel free to contact either the undersigned or Dr. Sharon Hamm at (770) 534-8239 if you have further questions.

Thank you.

Sincerely,



Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

CC: Nancy Chamberlain

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RECEIVED
JUL 27 1998
GENERIC DRUGS



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

July 30, 1998

N/AM

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER, Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: MINOR TELEPHONE AMENDMENT
ANDA 75-041: Isosorbide Mononitrate Extended-release Tablets, 60 mg
Bioequivalency Responses

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application for Isosorbide Mononitrate Extended-release Tablets, 60 mg (ANDA 75-041) received by the FDA Office of Generic Drugs on December 31, 1996. We would like to acknowledge receipt of your telefax dated July 29, 1998, which contained comments from the Division of Bioequivalence, a copy of which is provided in Attachment 1.

Please be advised that we have revised our finished product protocol to reflect the dissolution specifications and methods described in the July 29 telefax. A copy of the revised finished product protocol is provided in Attachment 2.

We now look forward to hearing from you regarding your requirements for proceeding with methods validation. Please feel free to contact either the undersigned or Dr. Sharon Hamm at (770) 534-8239 if you have further questions.

Sincerely,

Helen Ryan M.Sc.
Manager, Regulatory Affairs

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JUL 31 1998

GENERIC DRUGS



élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

July 24, 1998

ORIG AMENDMENT

PIVOTAL LOT
N/AE

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER, Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: TELEFAX AMENDMENT
ANDA 75-041: Isosorbide Mononitrate Extended-Release Tablets, 60 mg
Dissolution Testing & Specifications

Dear Mr. Sporn:

Reference is made to the pending Abbreviated New Drug Application for Isosorbide Mononitrate Extended-Release Tablets, 60 mg (ANDA 75-041). We would like to acknowledge receipt of your telefax dated July 23, 1998, which contained comments from the Division of Bioequivalence. As discussed with your representative (Mark Anderson) we would request your reconsideration of the proposed dissolution specifications. As was provided previously (July 1, 1998), we have conducted dissolution testing at the recently recommended condition on the pivotal lot (Lot #50C02A). On the basis of this data, we do not understand the proposed 4 and 8 hour specification ranges. For the 1/2 and 2 hour intervals, the specifications appear centered relative to the mean data for the pivotal lot. The 4 and 8 hour specifications however appear to be skewed relative to the pivotal lot data. Our review of the data would result in a recommended specification for the 4 and 8 hour intervals, which is more centered to the pivotal lot as follows:

4 hour: ...
8 hour: ...

For ease of comparison, a summary of the mean pivotal lot dissolution data, proposed Agency specifications, and our recommended alternates at the 4 and 8 hour intervals, are provided in the table below.

RECEIVED

JUL 27 1998

GENERIC DRUGS

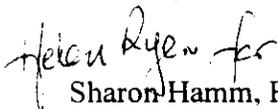
**ISOSORBIDE MONONITRATE ER 60 MG
DISSOLUTION AT 50 R.P.M./WATER**

Hours	Pivotal Lot #50C02A (Mean % Released)	FDA Proposed Specifications	Elan Proposed Alternate Specifications
1/2	15.9	10-30%	
1	23.9	--	
2	35.2	25-45%	
4	51.2	35-55%	
6	63.6	--	
8	73.9	60-80%	
10	81.3	--	
12	88.2	NLT 80%	

Although we understand that the proposed specifications are viewed as "interim" specifications, batches manufactured to date would have been produced utilizing the pivotal batch as a target. We are therefore concerned that the recommended shift at the 4 and 8 hour intervals as per the proposed specification, would pose difficulties.

We would appreciate your review of the proposed alternate specifications which are very clearly centered to the pivotal batch. We would welcome an opportunity to discuss this further with the reviewers, in an effort to expedite a conclusion in this regard. We thank you in advance for your consideration.

Sincerely,



Sharon Hamm, Pharm. D., R.Ph.
Senior Vice President
R&D Technical Operations

SH/bh

Attachment

JUL 16 1998

File # 7.1 28
No 7/15/98 etc

Isosorbide Mononitrate
60 mg Extended-Release Tablets
ANDA #75-041
Reviewer: Z.Z. Wahba
File #75041a2.298

Elan Pharmaceutical
Gainesville, GA
Submission Date:
July 01, 1998
July 15, 1998

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm has previously submitted three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple dose) comparing its test product Isosorbide Mononitrate Extended-Release (ER) Tablets, 60 mg to the reference listed product, Schering's Imdur® Extended Release Tablets, 60 mg. The submission was reviewed and was found incomplete by the Division of Bioequivalence (the submission dated Dec. 31, 1996, ANDA #75-041, reviewed by A. Patel) due to deficiency comments.
2. In this submission, the firm has responded to the dissolution, deficiency comments (review of an amendment dated 6/10/98) and included additional information in the current submission.

DEFICIENCY COMMENT

The firm was asked to submit comparative dissolution testing data conducted on a validation batch.

THE FIRM'S RESPONSE TO THE DEFICIENCY COMMENT (NOT TO BE RELEASED UNDER FOI):

The firm has clarified the issue regarding the bio-batch number as follows: All dissolution profile data provided in the submission refer to the same batch (Lot #50C02A/DB3776) of IS-5-MN ER test product, i.e., the bulk product was given the Batch/Lot #DB3776, which was packed in 100 count containers and given the Batch/Lot #50C02A. The test product bio-batch was manufactured on 09/29/95 and packed on 10/16/95. For the reference product Lot #5DJC1 was used for the dissolution data at 100 rpm and Lot #5DJC60 was used for the dissolution data at 50 rpm and 75 rpm. The expiry date for the reference product Lot # 5DJC1 was 12/96 and for Lot #5DJC60

was 4/98.

The firm has provided acceptable stability data for the test product up 31 months (see supplement dated July 01, 1998, attachment #3, pages 59-60).

Based on the dissolution data and the stability data submitted, the dissolution data are acceptable. The firm is required to submit comparative dissolution data from its next three fresh production batches. Those fresh batches should be compared to a validation batch of the reference listed drug. The dissolution testing should be done on whole tablet as well as half-tablet (as indicated in the review of an amendment dated 6/10/98).

RECOMMENDATIONS

1. The three in vivo bioequivalence studies, single-dose under fasting and non-fasting conditions, and steady-state multiple-dose conditions conducted by Elan Corp. on its Isosorbide Mononitrate ER Tablet, 60 mg, lot #50C02A, comparing it to Schering's Imdur® ER Tablet, 60 mg, have been found acceptable. The three studies demonstrate that under fasting, non-fasting and steady-state conditions, Elan's Isosorbide Mononitrate ER Tablets, 60 mg, are bioequivalent to Schering's Imdur® ER Tablet, 60 mg.
2. The dissolution testing conducted by Elan Corp. on its Isosorbide Mononitrate ER Tablet, 60 mg, lot #50C02A is acceptable. The dissolution testing should be conducted in 1000 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data the following tentative specifications are recommended for Isosorbide Mononitrate :

Whole Tablet

0.5	hour	NLT	and	NMT
2.0	hour	NLT	and	NMT
4.0	hours	NLT	and	NMT
8.0	hours	NLT	and	NMT
12	hours	NLT		

Half Tablet

0.5	hour	NLT	and	NMT
2.0	hour	NLT	and	NMT

4.0 hours NLT and NMT
8.0 hours NLT and NMT
12 hours NLT

The firm should be informed of the above recommendations.

/S/ a

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

AND 7/15/98

/S/

1/15/98

Concur:

/S/

Date: *7/16/98*

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

Isosorbide Mononitrate
60 mg Extended-Release Tablets
ANDA #75-041
Reviewer: Z.Z. Wahba
File #75041a3.798

Elan Pharmaceutical
Gainesville, GA
Submission Date:
July 24, 1998

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm has previously submitted three in vivo bioequivalence studies (single-dose fasting, single-dose post-prandial and multiple dose) comparing its test product Isosorbide Mononitrate Extended-Release (ER) Tablets, 60 mg to the reference listed product, Schering's Imdur® Extended Release Tablets, 60 mg. The submission was reviewed and was found acceptable by the Division of Bioequivalence (The review dated July 16, 1998).
2. In this telefax amendment, the firm has requested the Division of Bioequivalence to reconsider the proposed dissolution specifications. The firm proposes the following changes: at 4 hour and 8 hours intervals, the specification would be _____ and _____ respectively. The dissolution specifications that were communicated to the firm were _____ and _____, at 4 hour and 8 hours intervals, respectively.

COMMENT

Based on the generated dissolution data, the firm's request for changing its drug product dissolution specification at 4 and 8 hour intervals to be _____ and _____ respectively, is acceptable.

RECOMMENDATION

The dissolution testing conducted by Elan Corp. on its Isosorbide Mononitrate ER Tablet, 60 mg, lot #50C02A is acceptable. The dissolution testing should be conducted in 1000 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data the following tentative specifications are recommended for Isosorbide Mononitrate :

0.5 hour NLT and NMT ;
2.0 hour NLT and NMT

4.0 hours NLT and NMT
8.0 hours NLT and NMT
12 hours NLT

The firm should be informed of the above recommendations.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT

FT INITIALLED BDAVIT

7/29/98

/S/

9/98

Concur: _____

/S/

Date: 7/29/98

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

Isosorbide-5-Mononitrate
60 mg ER Tablet
ANDA # 75-041
Reviewer: A.P.Patel
File: x:\wpfile\biofinal\75041sd.d96

Elan Corp.
Gainesville, GA
Submission Date:
Dec. 31, 1996
March 10, 1997
June 2, 1997

Review of three bioequivalence studies and dissolution data

Background

The sponsor has submitted protocols for proposed bioequivalence studies on its (Elan's) isosorbide mononitrate 60 mg extended release tablets and the reference product, Imdur^R 60 mg tablets manufactured by Key/Schering-Plough. The Division of Bioequivalence has not issued guidance for the conduct of bioequivalence studies on isosorbide mononitrate (IS-5-MN).

IS-5-MN, an organic nitrate (1,4:3,6-dianhydro-D-glucitol 5-nitrate), is a vasodilator. Following oral administration as a solution or immediate-release tablets, maximum plasma concentrations of IS-5-MN are achieved in 30 to 60 minutes, with an absolute bioavailability of approximately 100%. It is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. IS-5-MN is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. The mean plasma elimination half-life of IS-5-MN is approximately 5 hours. Approximately 96% of the administered dose of IS-5-MN is excreted in the urine within 5 days and only about 1% is eliminated in the feces. At least six different compounds have been detected in urine, and metabolites are not pharmacologically active.

The pharmacokinetics and/or bioavailability of IS-5-MN extended release tablets (Imdur^R 60 mg) have been studied in both normal volunteers and patients following single- and multiple-dose administration. Data from these studies suggest that the pharmacokinetics of IS-5-MN administered as Imdur^R tablets are similar between normal healthy volunteers and patients with angina pectoris.

Bioavailability of Imdur^R Tablets 60 mg may be affected by the presence of food in the GI tract; concomitant food intake may decrease the rate (increase in T_{max}) but not the extent (AUC) of absorption of IS-5-MN.

A. BIOSTUDY: Single dose under fasting conditions #0395002

A-1. OBJECTIVE: To establish bioequivalence of Elan's 60 mg IS-5-MN tablets to the reference product, Imdur^R 60 mg tablets in a *single-dose* two treatment, two-sequence, two-phase, two-way crossover study following administration of test formulations under *fasting* conditions.

A-2. STUDY DATES: Jan. 6, 1996 - Jan. 24, 1996 (including post-study medicals)

A-3. FACILITIES: The study was performed following the protocol #0395002 under the supervision of Dr. Anthony Fitzpatrick at Elan Clinical Pharmacology Center, Monksland, Althone, Co. Westmeath, Ireland. Plasma samples were analyzed at:

A-4. SUBJECTS: Twenty four (24) male subjects (20-38 years) were enrolled for this study. The selection criteria for subjects participating in this study are as follows:

Inclusion criteria.

- Healthy male volunteers, 20-38 years of age with a mean age of 27 years.

- Free from clinical anomalies as judged by medical history, physical examination, and laboratory tests including hematology, clinical chemistry, urine analysis, 12-lead ECG, drug screen and virology.

Exclusion criteria:

- Participation in another study within the sixteen months preceding the trial, and use of prescription medicine within two weeks and non-prescription medication within one week of the study start.
- Deviation in excess of 10% from ideal body weight according to the Metropolitan Life Insurance Tables.
- History of drug abuse.
- Blood donation within 90 days prior to study entry.
- Smoking of >10 cigarettes per day.
- Subjects who have had surgery of GI tract which may interfere with absorption of study drug.
- History of hypersensitivity to study drug or related compounds.
- Systolic blood pressure <100 mm Hg or diastolic blood pressure <60 mm Hg.

A-5. ETHICAL CONSIDERATIONS

Informed consent: The subjects were required to read and sign a consent form prior to enrollment.

Indication for subject withdrawal: Subjects were free to withdraw at anytime, or they may be withdrawn if necessary to protect their health. Any such withdrawals were documented.

Institutional review board: This protocol was reviewed by the Institutional Review Board (IRB), the National Drug Advisory Board and the Department of Health.

A-6. CLINICAL CONDUCT OF THE STUDY

Housing and drug administration: Subjects reported to the clinic between 17:00 and 18:00 hours on the evening of Day-1 (a day before the dosing time) of period one of the study. They were required to provide three urine samples for drugs of abuse screen. During each treatment period, duration of a volunteer stay in the clinic was 16 hours before dosing on day one and for 36 hours after the last dose of medication on day 5, a total of 148 hours in each phase of the study. The two study phases were separated by a period of ≥ 7 days.

Following an overnight fast (10 hours) subjects were administered assigned formulations between 8:00 -10:00 AM with 240 ml of water based on the following computer generated randomization sequence:

SEQUENCE	SUBJECT NUMBER
A B	1,4,6,7,11,12,16,18,20,21,22,24
B A	2,3,5,8,9,10,13,14,15,17,19,23

where:

A: Eian's IS-5-MN 60 mg tablet, Lot#50C02A.

B: Imdur^R 60 mg tablet (Key/Schering-Plough), Lot#5DJC1 (US Source)

Each treatment period lasted approximately 52 hours, with a washout period of seven days between each treatment period.

Food: During each treatment period, subjects fasted overnight before dosing. On each dosing day lunch was served 4 hours after dosing, an evening meal at 9 hours after drug administration and a light supper at 12 hours after treatment. On day 2 breakfast was served at approximately 9:30 hours followed by lunch at 13:00 hours and an evening meal at 18:00 hours. The same daily menus were followed in each treatment period.

Blood sampling: Blood samples (7 ml) were collected in vacutainers containing lithium heparin at 0 hours (pre-dose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 12, 16, 20, 24 and 36 after dosing. Blood samples were centrifuged, plasma separated and stored at -20°C till assayed.

Safety and adverse reaction monitoring: To monitor safety, sitting blood pressure and pulse was measured before dosing and at approximately at 0.5, 1, 2, 4, 8, 12, 16, 24, 30 and 36 hours after dosing. A 12-lead ECG was performed during screening and at 24 hours after dosing. Throughout confinement, subjects were monitored by a medically qualified person, for adverse reactions to the study formulations and/or procedures. All adverse reactions were documented.

A-7. ANALYTICAL METHODOLOGY: Plasma samples were analyzed for IS-5-MN with chromatography. Isosorbide-2-nitrate (IS-2-MN) is the internal standard. The limit of quantitation of the assay was 4.01 ng/ml (CV=4%) and values below this limit were assigned a value of zero. Sensitivity limit was 2.0 ng/ml. There was no interference at retention times of IS-5-MN or IS-2-MN from blank samples.

Assay: The standard curve was linear up to 481 ng/ml. Mean (n=13) calibration line had correlation of 0.9968, slopes of 0.00667 and an intercept of 0.00385. The intra-day variability for concentrations calculated with back calculation (CV%; n=5) at 4.01, 6.41, 12, 36, 120 and 360 ng/ml was 10, 4.58, 8.06, 5.69, 2.31 and 6.21, respectively. The inter-day variability for concentrations calculated with back calculation (CV%; n=5) at 4.01, 6.41, 12, 36, 120 and 360 ng/ml was 17.5, 4.51, 13.2, 8.36, 4.59 and 9.91, respectively. The overall absolute recovery of IS-5-MN was 80.8% (s.d.=13.8). The overall absolute recovery of the internal standard was 58.4% (s.d.=7.32).

Stability:

3 Freeze-thaw cycles show recovery errors of -4.04% at 6.41 ng/ml and -15.1% at 360 ng/ml. Therefore, repeated freeze and thaw cycles should be avoided.

Long-term stability: samples stored frozen at -20°C for 3 months were stable. Samples left to stand and then processed after 4 hours at room temperature showed significant degradation. The recovery errors of -8.75% at 6.41 ng/ml, -10.4% at 36 ng/ml and -3.1% at 360 ng/ml.

Stability under assay conditions: IS-5-MN is not stable 24 hours in the processed samples at room temperature. To avoid degradation the analytical run contained 80 samples (80 samples=ca 10 hours between first and last sample).

The assay and stability data are acceptable.

A-8. PLASMA DATA ANALYSIS: Following pharmacokinetic parameters were analyzed, $AUC_{(0-36h)}$, $AUC_{(0-infinity)}$, $F_{(0-infinity)}$ (%), C_{max} , T_{max} , K_{el} and $t_{1/2}$, under fasting conditions (Table 1).

A-9. STATISTICAL ANALYSIS: ANOVA was performed on the pharmacokinetic parameters

using SAS-GLM according to the Division of Bioequivalence Guidance on Statistical Procedures for Bioequivalence (July 1992). The following sources of variation were included in the model: sequence, subjects nested in sequences, period and treatment. The 90% confidence intervals were determined for the log-transformed data (Table 3).

In vivo Results:

Twenty-four (24) male subjects (20-38 years) were enrolled and all of them completed the study.

All adverse reactions were documented. A total of 58 events were reported by 22 subjects. Only subjects #2 and #10 did not complain of any events. Subject #19 on treatment B (RLD) vomited 5 hours after the dosing. Of the events reported 48% were associated with test and 52% with a reference product. All events were considered mild or moderate in severity.

The plasma concentrations, pharmacokinetic parameters and statistical results for IS-5-MN are summarized below:

Table 1. Mean Plasma data for Test and Reference and PK Parameters

IS-5-MN Mean Plasma Data					
Time (h)	Test		Reference		Ratio T/R
	Mean	CV%	Mean	CV%	
0	0	0	0	0	0
0.50	137.43	30.86	167.82	43.78	0.82
1.00	218.88*	27.80	266.26	33.39	0.82
1.50	269.83*	25.75	345.28	30.54	0.78
2.00	300.83*	20.43	367.64	29.81	0.82
3.00	349.71*	23.95	415.63	30.73	0.84
4.00	381.67*	24.38	468.74	28.06	0.81
5.00	376.92*	25.11	453.17	29.58	0.83
6.00	372.38*	28.24	437.29	29.03	0.85
8.00	322.21*	24.58	386.08	28.87	0.83
12.00	239.46	30.87	270.21	29.14	0.89
16.00	151.38	37.83	160.84	31.02	0.94
20.00	104.65	35.19	94.62	35.27	1.11
24.00	66.65	47.36	59.10	37.27	1.13
30.00	25.58	54.46	21.65	40.04	1.18
36.00	9.70	56.43	9.08	56.23	1.07

PK Parameters	Test		Reference		Ratio T/R
	Mean	CV%	Mean	CV%	
Ratio of AUC (t/inf)	0.99	0.46	0.99	0.66	1.00
AUCt	**5669.98	24.83	6377.38	26.34	0.89
AUCinf	**5732.69	24.93	6443.30	26.35	0.89
Cmax	**409.25	24.83	495.96	26.68	0.83
Tmax	5.25	24.00	4.54	29.56	1.16
Thalf	4.33	9.82	4.59	18.04	0.94
Kel	0.16	9.92	0.16	17.97	1.04

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Thalf=h, Kel=h⁻¹;

*statistically significant, p < 0.05, compared to reference;

** p < 0.01 compared to reference

Table 2. Individual ratios of AUC_t vs AUC_{inf} for test and reference product

Subject #	Test AUC(t/inf)	Reference AUC(t/inf)	Ratio T/R
1	1.00	0.99	1.01
2	0.98	0.98	0.99
3	0.99	0.99	0.99
4	0.99	0.99	1.00
5	0.98	0.97	1.02
6	0.99	0.99	1.00
7	0.99	1.00	1.00
8	0.99	0.99	1.01
9	1.00	1.00	1.00
10	0.99	0.99	0.99
11	0.99	0.99	1.00
12	0.99	0.99	1.00
13	0.99	0.99	1.00
14	0.98	0.99	0.99
15	0.99	1.00	1.00
16	0.99	0.99	1.00
17	0.99	0.99	1.00
18	0.99	1.00	0.99
19	0.99	0.98	1.01
20	0.99	0.99	1.00
21	0.99	0.99	1.00
22	0.99	0.99	1.00
23	0.99	0.99	1.00
24	0.99	0.99	1.00
Mean	0.99	0.99	1.00
CV%	0.46	0.66	0.64
N	24	24	24

The AUC_t/AUC_{inf} ratios for treatments for the fasting study are acceptable.

Figure 1: Mean Plasma IS-5-MN Concentrations

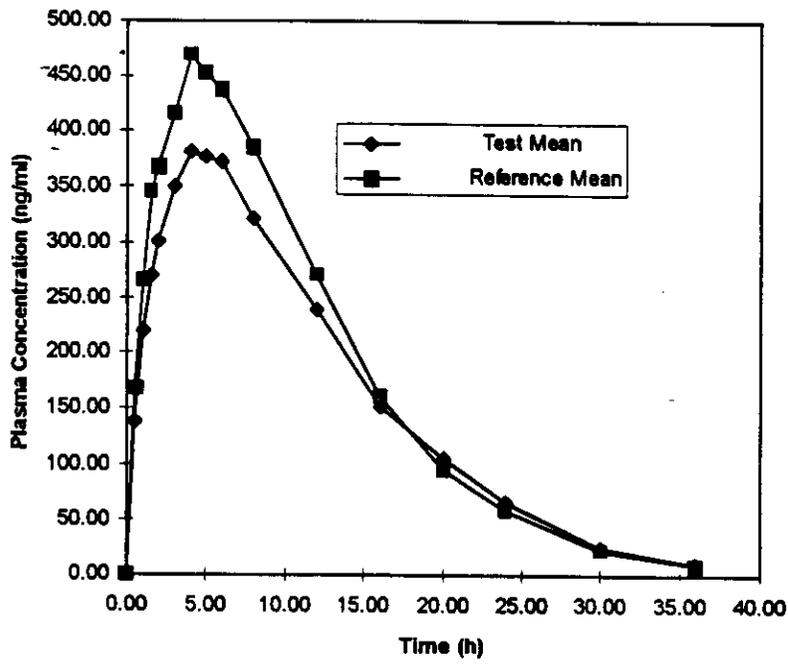


Figure 2: Mean Plasma IS-5-MN Concentrations (semi-log plot)

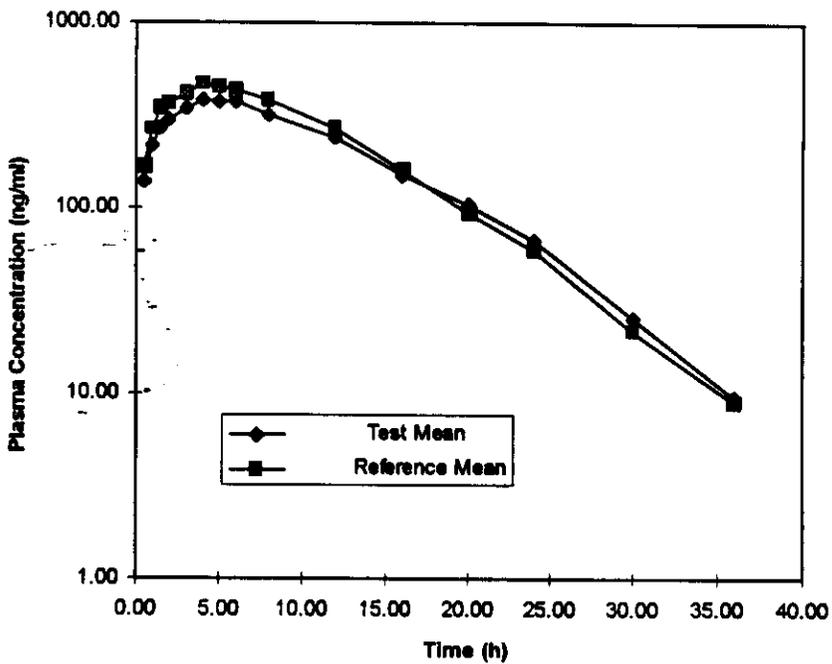


Table 3. Log-transformed PK Parameters and 90% Confidence intervals

PK Parameter	LSMEANS		Ratio T/R	90% C.I.	
	Test	Reference		Lower	Upper
LAUC _t	8.614	8.727	0.89		
LAUC _{inf}	8.625	8.737	0.89		
LG _{max}	5.984	6.168	0.83		

Units: AUC=ng.h/ml, C_{max}=ng/ml;

The fasting study ln-transformed PK Parameters meets the 90% confidence limits of between 80-125%. The study is acceptable.

There was a significant treatment difference in the shape of the plasma concentration versus time curves. The test IS-5-MN plasma levels are significantly lower than reference between 1 and 8 hours. From 12 to 36 hours post-dosing, there was no significant treatment difference in the plasma concentrations data. ANOVA analysis detected a significant treatment difference between the two formulations. However, the 90% confidence intervals for AUC and C_{max} are in the 80 - 125% range. The AUC (0-t/inf) ratios for test and reference are similar. The Tmax and the elimination constants were also similar for the two treatments.

The firm has also collected pharmacodynamic data, heart rate, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and reference are similar. The data were statistically analyzed using SAS-GLM repeated measures ANOVA. There was no clinically significant treatment difference in either the diastolic or systolic blood pressure or in the heart rate data for this study.

B. Steady State Bio-Study #0395001

B-1. OBJECTIVE: To compare the *steady state* bioequivalence of Elan's IS-5-MN 60 mg tablets to the reference product, Imdur^R 60 mg tablets in a two-treatment, two-sequence, two-phase, two-way crossover study following *once-daily* administration of test formulations under *fasting* conditions.

B-2. STUDY DATES: Nov. 30, 1995 - Dec. 22, 1995.

B-3. FACILITIES: Please see fasting study.

B-4. SUBJECT SELECTION: Twenty-four (24) male subjects (20 - 39 years) were enrolled for this study. For selection criteria for subjects participating in this study please see fasting study. Subject #10 was found positive for alcohol in the pre-study examination and was dropped. Subject #15 completed period one (Imdur) but was found to have elevated blood pressure before dosing in period two and was discontinued. Subjects R3 and R2 replaced subjects #10 and 15, respectively.

B-5. ETHICAL CONSIDERATIONS: Please see fasting study.

B-6. CLINICAL CONDUCT OF THE STUDY

Housing and drug administration: Subjects reported to the clinic between 17:00 and 18:00 hours on the evening of Day-1 (a day before the dosing time) of period one of the study. They were required to provide three urine samples for drugs of abuse screen. During each treatment period, duration of a volunteer stay in the clinic was 16 hours before dosing on day one and for 36 hours after the last dose of medication on day 5, a total of 148 hours in each phase of the study. The two study phases were separated by a period of ≥ 7 days.

Following an overnight fast (10 hours) on days 1-5, subjects were administered assigned formulations between 8:00 -10:00 A.M. with 240 ml of water based on the following computer generated randomization sequence:

SEQUENCE	SUBJECT NUMBER
A B	3,8,9,10(R2),11,12,13,14,17,19,22,23
B A	1,2,4,5,6,7,15 (R3),16,18,20,21,24

where:

A: Elan's IS-5-MN 60 mg tablet lot# 50C02A

B: Imdur^R 60 mg tablet (Key/Schering-Plough) lot# 5DJC1

Food: During each treatment period, subjects fasted overnight before dosing. On each dosing day lunch was served 4 hours after dosing, an evening meal at 9 hours after drug administration and a light supper at 12 hours after treatment. On day 2 breakfast was served at approximately 9:30 hours followed by lunch at 13:00 hours and an evening meal at 18:00 hours. The same daily menus were followed in each treatment period.

Blood sampling: Blood samples (7 ml) were collected in vacutainers containing lithium heparin at 0 hours (pre-dose) on day 1-5, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6,

12, 16, 20, 24 and 36 after dosing on day 5. Blood samples were centrifuged, plasma separated and stored at -20°C till assayed.

Safety and adverse reaction monitoring: To monitor safety, sitting blood pressure and pulse were measured before dosing and at approximately at 0.5, 1, 2, 4, 8, 12 and 16 hours on days 1-4, and at 0.5, 1, 2, 4, 8, 12, 16, 24, 30 and 36 hours after the day-5 dosing. A 12-lead ECG was performed during screening and at 24 hours after dosing on day 5. Throughout confinement, subjects were monitored by a medically qualified person, for adverse reactions to the study formulations and/or procedures. All adverse reactions were documented.

B-7. ANALYTICAL METHODOLOGY: Please see fasting study.

B-8. PLASMA DATA ANALYSIS: Following pharmacokinetic parameters were analyzed, $AUC_{(0-t)}$, C_{max} , T_{max} , C_{min} , C_{av} , fluctuation, K_{el} and $t_{1/2}$, under steady-state conditions (Table 4).

B-9. STATISTICAL ANALYSIS: Steady-state attainment for each subject for days 3, 4, and 5 was determined by linear regression to show that the slope values were not significantly different from zero. Analysis of variance for AUC and C_{max} and 90% confidence intervals using the log-transformed data (Table 5).

In vivo Results:

Twenty-four (24) male subjects (20 - 39 years) were enrolled for this study. For selection criteria for subjects participating in this study please see fasting study. Subject #10 was found positive for alcohol in the pre-study examination and was dropped. Subject #15 completed period one (Imdur) but was found to have elevated blood pressure before dosing in period two and was discontinued. Subjects R3 and R2 replaced subjects #10 and 15, respectively.

Adverse events: Total of 225 events were reported by 23 subjects. Only subject 4 did not complain of any adverse events. 136 of these adverse events were reported in period one and 89 in period two. 45% of the adverse events were associated with treatment A (test) and 55% were associated with treatment B (reference). Majority of the adverse events reported were for headaches. Others included nausea/upset stomach, feeling of tension at the back of the neck and cramps.

The plasma concentrations, pharmacokinetic parameters and statistical results for IS-5-MN are summarized below:

Table 4. Mean IS-5-MN Plasma data for Test and Reference and PK Parameters

Time (h)	Test		Reference		Ratio T/R
	Mean	CV%	Mean	CV%	
0	0.40	489.90	0.00	0.00	0.00
24	78.34	65.87	67.37	50.91	1.16
48	74.90	52.18	67.70	51.35	1.11
72	78.98	47.48	65.66	64.44	1.20
96	73.97	44.08	70.18	49.21	1.05
96.5	268.29	45.79	295.61	56.99	0.91
97	319.58	28.84	394.13	46.08	0.81
97.5	407.63	31.06	500.58	35.01	0.81
98	403.50	25.65	514.33	33.38	0.78

99	495.21	28.56	564.96	31.37	0.88
100	539.58	25.63	538.92	30.39	1.00
101	495.50	24.93	499.21	30.83	0.99
102	468.13	25.67	488.38	24.92	0.96
104	397.29	30.49	407.17	28.85	0.98
108	268.21	32.93	295.38	37.18	0.91
112	176.12	39.43	174.78	44.19	1.01
116	130.85	52.07	116.73	48.68	1.12
120	83.13	60.83	70.70	85.06	1.18
124	33.21	77.31	31.24	84.84	1.06
136	15.37	90.29	10.52	81.46	1.46

Units: C_{max}=ng/ml AUC=ng.h/ml

PK Parameter	Test		Reference		Ratio T/R
	Mean	CV%	Mean	CV%	
Cmax	568.92*	24.88	632.67	28.35	0.90
Tmax	4.08	20.32	3.63	47.48	1.13
Cmin	82.92	60.52	64.29	62.76	1.29
Tmin	23.08	19.45	23.83	3.43	0.97
Cav	279.47	27.27	293.52	28.89	0.95
AUC _{0-t}	6707.26	27.27	7044.51	28.89	0.95
Thalf	4.99	24.92	5.11	26.48	0.98
Kel	0.15	22.20	0.14	21.22	1.03
Cmax/Ct	9.23	61.40	12.95	59.57	0.71
cmax-cmin	486.00	23.01	568.38	29.47	0.86
cmax/c24h	9.24	61.32	13.03	58.24	0.71
(cmax-cmin)/cmin	8.24	68.76	12.03	63.08	0.68
(cmax-cmin)/cav	1.80	22.92	1.99	23.99	0.90

* significant ,p<0.05, compared to ref.

Table 5. Log-transformed PK Parameters and 90% Confidence intervals

PK Parameter	LSMEANS		Ratio T/R	90% C.I.	
	Test	Reference		Lower	Upper
LAUC _t	8.775	8.819	0.96		1
LC _{max}	6.315	6.413	0.91		3

Units: AUC=ng.h/ml, C_{max}=ng/ml

Analysis with Subject#8 removed

PK Parameter	LSMEANS		Ratio T/R	90% C.I.	
	Test	Reference		Lower	Upper
LAUC _t	8.778	8.815	0.96		
LC _{max}	6.320	6.411	0.91		

Units: AUC=ng.h/ml, C_{max}=ng/ml

Figure 3: Mean Plasma IS-5-MN Concentrations

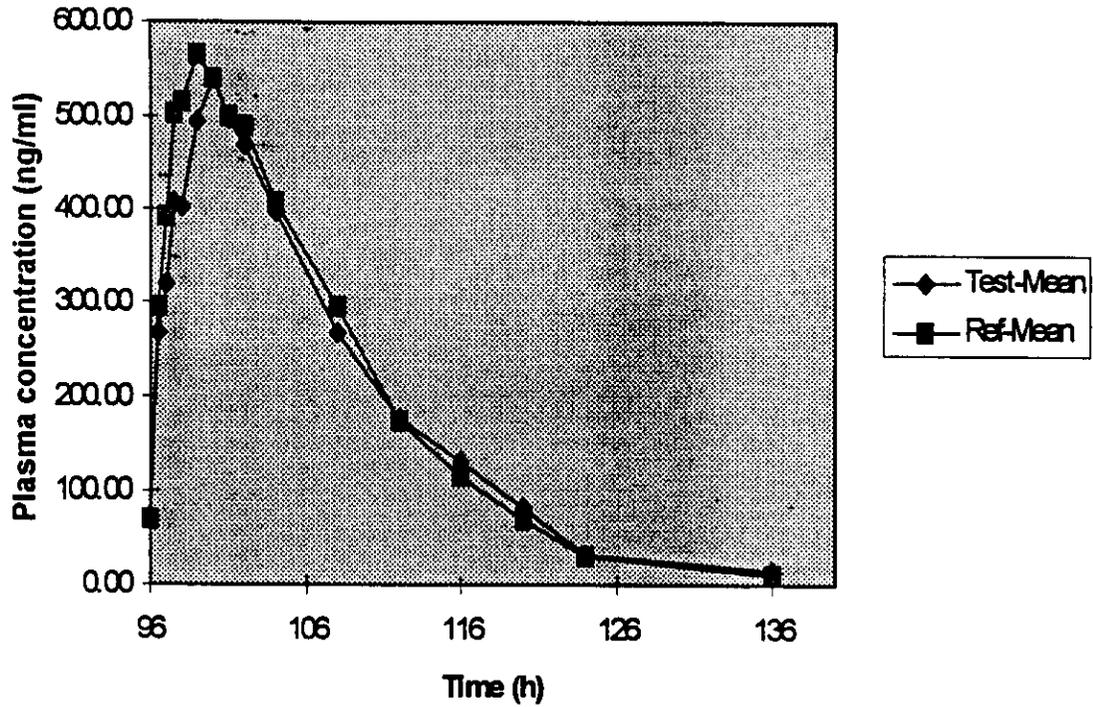
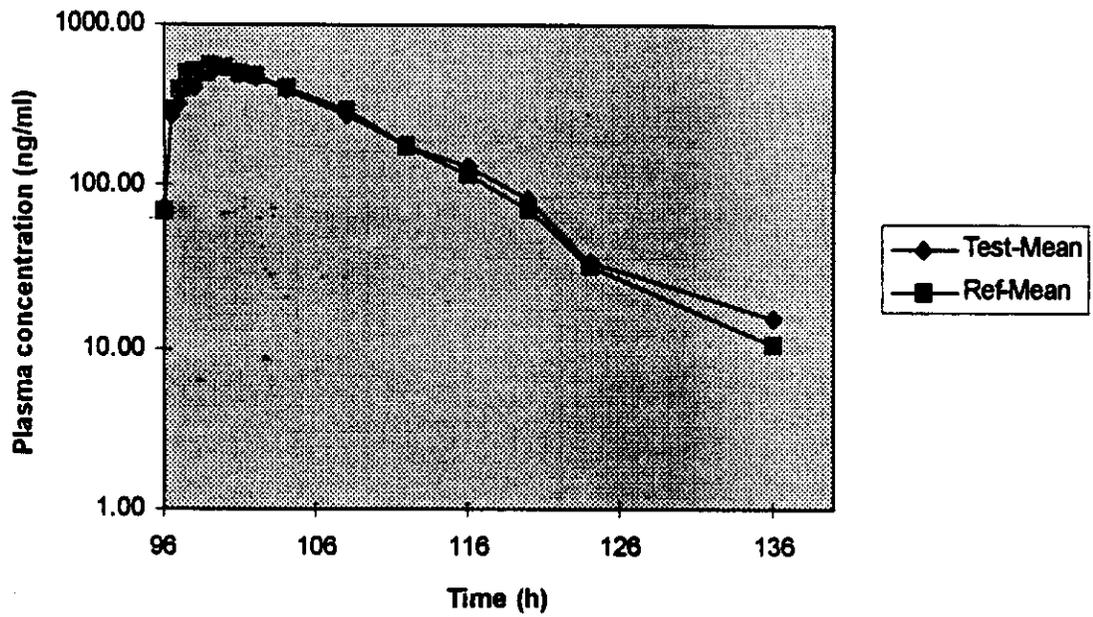


Figure 4: Mean Plasma IS-5-MN Concentrations (semi-log plot)



The steady-state study ln-transformed PK Parameters meets the 90% confidence limits of between 80-125%. The study is acceptable.

There was a significant ($p < 0.05$) difference in the plasma concentration between the two treatments at the 98-hour sampling time point. There was no significant difference in the steady state trough (120 hours; C_{24ss}) plasma concentrations. The sampling time points at 72, 96 and 120 hours were used to decide attainment of steady state for each subject by linear regression. Steady state is reached if the slope of the line through the time points is not significantly different from zero. For subject #7, linear regression could not be conducted due to a missing 96-hour sample following treatment A (test). The slope of the line through the 24, 48 and 72 hours for this subject was not significantly different to zero. For subject #8 the slope of the line through the 72, 96 and 120 hour time points was greater than zero. However, the linear regression through the pooled 72, 96 and 120 hour samples for each treatment showed that the slopes were not significantly different from zero. The 90% confidence intervals are within the 80 - 125% for $\ln AUC_{0-24}$ and $\ln C_{max}$ without subject#8 data.

The peak plasma concentrations were observed at similar times for the two formulations and there was no difference in the average plasma concentrations over the 24-hour steady state period between the products. Significant differences were found for indices of peak-to-trough fluctuations between the two formulations due to slight differences in trough (C_{min}) and peak plasma concentrations observed with the test formulation. However, the overall shape of the plasma-time curves were similar with no difference in plasma concentrations at the end of the dosing interval (C_{24ss}) for the two formulations. Analysis found no treatment difference in the apparent elimination rate. The 90% confidence intervals are within the 80 - 125% for $\ln AUC_{0-24}$ and $\ln C_{max}$ (in presence or absence of subject#8 data). The study is acceptable.

The firm has also collected pharmacodynamic data, heart rate, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and reference formulations are similar. The data was statistically analyzed using SAS-GLM repeated measures ANOVA. There was no clinically significant treatment difference in either the diastolic or systolic blood pressure or in the heart rate data for this study.

C. Bioavailability Study: Single dose administered under non fasting conditions, study #0295010

C-1. OBJECTIVE: To compare the bioavailability of Elan's IS-5-MN 60 mg tablets to the reference product, Imdur^R 60 mg tablets in a single-dose, three-treatment, six -sequence, three-phase, three-way crossover study following administration of test formulations after consumption of a high fat content meal.

C-2. STUDY DATES: Jan. 08, 1996 - Feb. 09, 1996

C-3. FACILITIES: Please see A-3.

C-4. SUBJECT SELECTION: Twenty-four (24) subjects (20 - 38 years) were enrolled for this study. The selection criteria for subjects participating in this study are the same as mentioned in A-4. Subject #08 withdrew from the study for reasons unrelated to the study and was replaced with standby subject#108.

C-5. ETHICAL CONSIDERATIONS: Please see A-5.

C-6. CLINICAL CONDUCT OF THE STUDY

Housing: Same as A-6.

Drug Administration: Following a 10 hour overnight fast subjects received an Elan 60 mg IS-5-MN tablet under either fasting and non fasting (high fat meal 15 minutes before dosing, according to Guidance for Oral Extended (Controlled) Release Dosage Forms In Vivo Bioequivalence and In Vitro Dissolution Testing, September 1993) conditions or Imdur^R 60 mg tablet under non fasting conditions.

Subjects were administered assigned formulations with 240 ml of water based on the following computer generated randomization sequence:

SEQUENCE	SUBJECT NUMBER
A BC	6,9,13,23
B CA	1,5,7,22
C AB	12,18,21,24
A CB	2,14,15,17
C BA	108,11,16,20
B AC	3,4,10,19

Where:

A: Elan's IS-5-MN 60 mg tablet (lot#50C02A) under fasting conditions.

B: Elan's IS-5-MN 60 mg tablet (lot#50C02A) under non fasting conditions.

C: Imdur^R 60 mg tablet (lot#5DJC1) under non fasting conditions.

Food: The same as that given for the fasting study except the breakfast given to subjects receiving treatments B and C.

Blood sampling: Same as that given for the fasting study.

Safety and adverse reaction monitoring: Please see A-6.

C-7. ANALYTICAL METHODOLOGY: Please see A-7.

C-8. DATA ANALYSIS: Same as that given for the fasting study. A comparable food effects were assumed if the AUC and Cmax data for the test product remain within $\pm 20\%$ of that of the reference product. (Table 6).

C-9. STATISTICAL ANALYSIS: ANOVA was performed on the pharmacokinetic parameters using SAS-GLM according to the Division of Bioequivalence Guidance on Statistical Procedures for Bioequivalence (July, 1992).

In vivo Results:

Twenty-four (24) subjects (20 - 38 years) were enrolled for this study. Subject #08 withdrew from the study for reasons unrelated to the study and was replaced with standby subject#108.

Adverse Events: A total of 77 adverse events were reported. 35% were reported with treatment A, 30% were reported with treatment B and 35% were reported with treatment C. Subject #3 vomited 9-hours post dose on treatment C. The most common adverse event reported, 91%, was for headaches.

The plasma concentrations, pharmacokinetic parameters and statistical results for IS-5-MN are summarized below:

Table 6. Mean Plasma data for Test and Reference and PK Parameters under non fasting conditions: Mean, CV% and Ratios; N= 24 subjects.

Time (h)	Test-fasting		Test-non fasting		Reference-non fasting		RATIOS			
	Mean	CV%	Mean	CV%	Mean	CV%	T (fast) vs T(non Fast)	T (fast) vs R (non Fast)	T(non fast) vs R (non Fast)	
0	0	0	0	0	0	0	0	0	0	
0.5	125.05	36.86	58.33*	70.09	72.55	56.06	2.14	1.72	0.80	
1	192.71	28.04	146.00*	48.81	162.80	46.90	1.32	1.18	0.90	
2	313.13	25.91	227.34*	36.71	249.33	34.26	1.38	1.26	0.91	
3	335.46	25.87	312.13	31.04	307.25	27.90	1.07	1.09	1.02	
4	326.67	28.66	341.50	24.37	369.92	36.43	0.96	0.88	0.92	
5	327.71	25.39	356.25	25.66	381.63	28.10	0.92	0.86	0.93	
6	318.67	32.12	360.13	30.78	367.04	28.46	0.88	0.87	0.98	
7	291.46	31.62	334.83*	28.89	363.13	27.86	0.87	0.80	0.92	
8	282.33	31.22	321.08	31.34	364.46	27.80	0.88	0.77	0.88	
9	252.06	30.74	304.36*	29.05	324.29	30.27	0.83	0.78	0.94	
10	221.75	28.78	277.89*	27.88	308.88	27.21	0.80	0.72	0.90	
12	191.57	35.01	220.59	36.50	241.50	33.03	0.87	0.79	0.91	
16	119.14	36.88	148.85	45.95	145.75	35.01	0.80	0.82	1.02	
20	76.62	46.23	88.34	54.06	90.58	37.35	0.87	0.85	0.98	
24	48.98	47.14	53.90	62.06	55.16	48.04	0.91	0.89	0.98	
30	17.71	51.24	21.22	66.52	18.79	42.73	0.83	0.94	1.13	
36	7.21	63.20	8.89	77.82	7.48	63.85	0.81	0.96	1.19	
							Min	0.80	0.72	0.80
							Max	2.14	1.72	1.19

* significantly different from fasting conditions.

Table 6. Contd.

PK Parameter	Test-fasting		Test- non fasting		Reference- non fasting		Ratios T-nf/R-nf
	Mean	CV%	Mean	CV%	Mean	CV%	
AUCt	4717.69	27.64	5147.23	28.96	5429.55	26.76	0.95
AUCinf	4772.56	27.77	5222.13	28.90	5486.36	26.79	0.95
Cmax	383.42	24.95	406.21	22.47	428.29	30.35	0.95
Tmax	3.92	40.49	5.54	34.48	5.25	31.90	1.06
Thalf	4.75	12.01	4.70	19.69	4.62	11.14	1.02
Kel	0.15	11.67	0.15	19.22	0.15	12.37	1.00
Ka	0.38	42.74	0.25	42.35	0.26	38.49	0.96
MRT	10.20	10.64	10.84	13.83	10.61	7.88	1.02

Units: AUC=ng.h/ml, C_{max}=ng/ml, T_{max}=h, Thalf=h, Kel=h⁻¹

Table 7. Individual ratios of AUCt vs AUCinf for test and reference product

Subject #	Ratios		
	Test-fast AUC(t/inf)	Test-non fast AUC(t/inf)	Reference AUC(t/inf)
1	0.99	0.99	0.99
2	0.99	1.00	1.00
3	0.98	0.99	0.99
4	0.98	0.99	0.99
5	0.99	0.99	0.99
6	0.99	0.99	0.99
7	0.99	0.99	0.99
8	0.98	0.99	0.99
9	0.99	0.99	0.99
10	0.99	0.99	0.99
11	0.99	0.98	0.98
12	0.99	0.98	0.99
13	0.98	0.98	0.99
14	0.99	0.94	0.99
15	0.98	0.99	0.99
16	0.99	0.99	0.99
17	0.99	0.96	0.99
18	0.99	0.99	0.99
19	0.99	0.98	0.98
20	0.99	0.99	0.99
21	0.99	1.00	1.00
22	0.99	0.99	0.99
23	0.99	0.99	0.98
24	0.99	1.00	1.00
Mean	0.99	0.99	0.99
CV%	0.39	1.19	0.35
N	24	24	24

The AUC_t/AUC_{inf} ratios for all three phases of the non fasting study are acceptable.

Figure 5: Mean Plasma IS-5-MN Concentrations

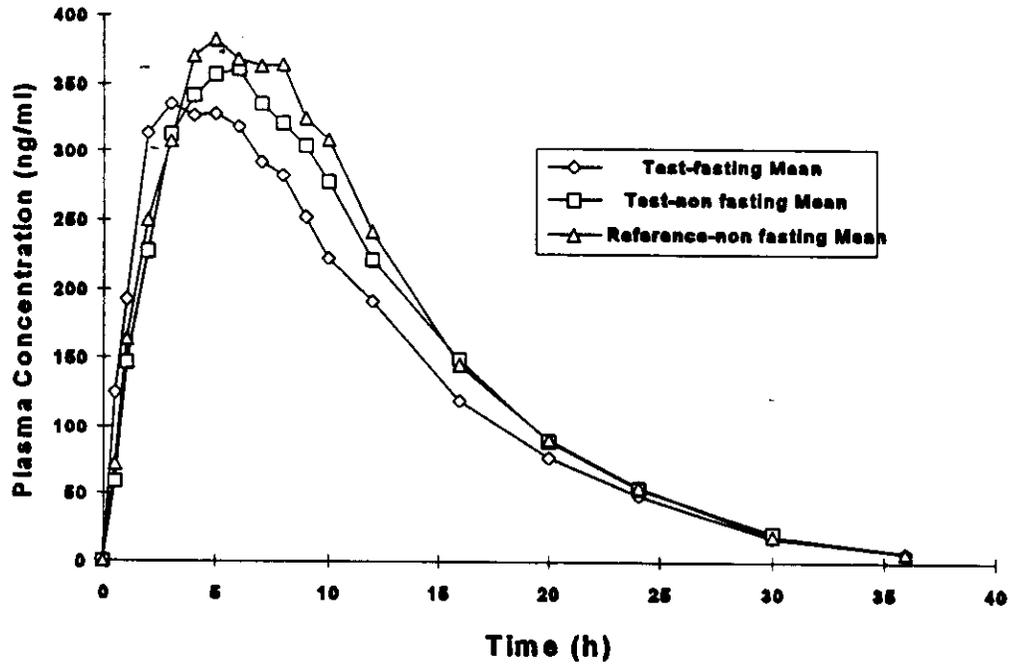


Figure 6: Mean Plasma IS-5-MN Concentrations
Semi-log plot

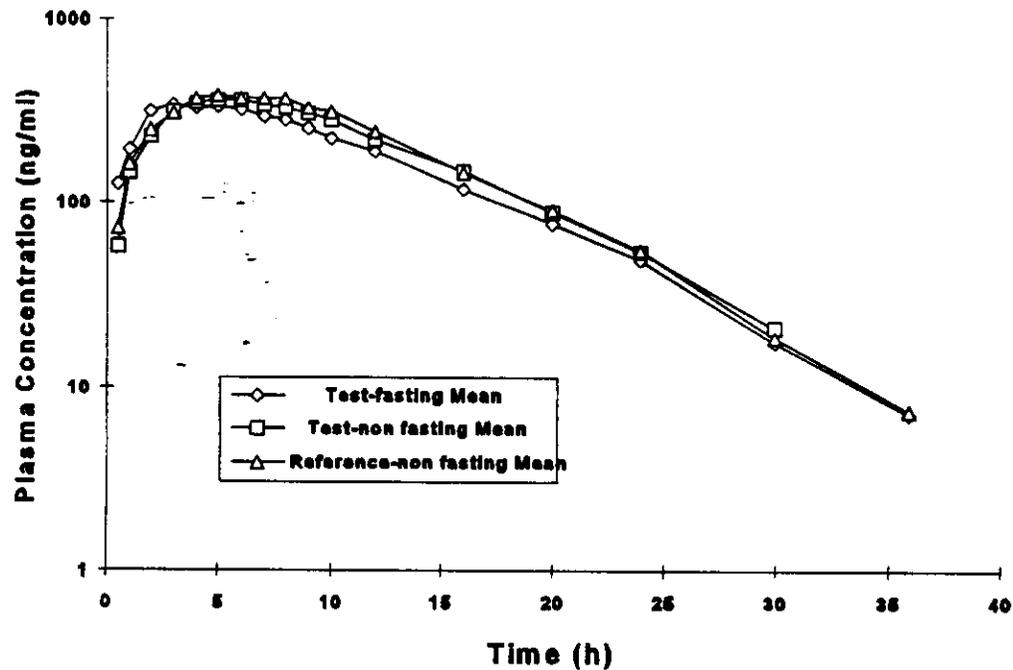


Table 8. PK Parameters and Test/Reference Ratios

PK Parameter	Test-fasting		Test- non fasting		Ref- non fasting		Ratios T-nf/R-nf
	Mean	CV%	Mean	CV%	Mean	CV%	
AUCt	4717.69	27.64	5147.23	28.96	5429.55	26.76	0.95
AUCinf	4772.56	27.77	5222.13	28.90	5486.36	26.79	0.95
Cmax	383.42	24.95	406.21	22.47	428.29	30.35	0.95
Tmax	3.92	40.49	5.54	34.48	5.25	31.90	1.06
Thalf	4.75	12.01	4.70	19.69	4.62	11.14	1.02
Kel	0.15	11.67	0.15	19.22	0.15	12.37	1

Units: AUC=ng.h/ml, C_{max}=ng/ml, Tmax=h, Thalf=h, Kel=h⁻¹

The ratio of test vs reference for the mean AUC(0-t), AUCinf and Cmax are 0.95 under non fasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax. The nonfasting study is acceptable.

The peak plasma concentrations were observed at different times following fasting and nonfasting administration. Peak concentrations were observed at 3.92 hours under fasting conditions and 5.3 -5.5 hours under nonfasting conditions. There were some differences in plasma concentration for test formulation under fasting and nonfasting conditions. The plasma concentrations between test and reference formulation were not significantly different. The difference in Cmax under nonfasting conditions between test and reference was -5.2%. There was no significant treatment difference in the apparent elimination rates for test formulation under fasting and nonfasting conditions. The high fat diet slowed the rate of absorption but did not affect the extent of absorption from the test and reference formulations. There was no treatment difference in any of the pharmacokinetic parameters under the nonfasting conditions. The ratios for AUCt, AUCinf and Cmax are within ± 20%. The study is acceptable.

The firm has also collected pharmacodynamic data, heart rate, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and reference formulations are similar. The data was also statistically analyzed using SAS-GLM repeated measures ANOVA. There was no clinically significant treatment difference in either the diastolic or systolic blood pressure or in the heart rate data for this study.

Product information:

Formulation:

Ingredient	mg/tablet
Isosorbide-5-Mononitrate (on lactose)	75.0*
Hydroxypropyl Methylcellulose	
Microcrystalline Cellulose	
✓ Magnesium Stearate	
✓ Colloidal Silicon Dioxide	

* Equivalent to 60mg of Isosorbide-5-Mononitrate

Batch size: theoretical batch of units.

Content uniformity: As per USP<905>

Test (lot#50C02A) Mean 60.5 mg/tablet;
Range: of label claim
CV%: 1.2%
Assay: 59.6 mg/tablet; 99.3% of label claim

Reference (lot# 5DJC1): content uniformity information not supplied.
Assay: 59.3 mg/tablet; 98.9% of label claim

In vitro Dissolution Test:

At present, USP dissolution method for IS-5-MN is not available. The firm has used in house dissolution method based on Guidance for In-Vitro Dissolution Testing and proposed dissolution specifications. The firm has conducted dissolution of test and reference products in buffered media of pH between pH 1.2 - 7.2 (attached), media were prepared as per USP except for pH 4 which was prepared with-citric acid and sodium monobasic phosphate. The graphs of dissolution profile shows an incorrect x-axis scale (no break in the axis) and instead of a 22 hour data point 24 hour data point is shown (see attached), needs clarification.

The dissolution of test and reference products were independent of pH. Since the dissolution profiles of the test and the reference products are similar, there is no evidence of dose dumping.

The firm has also conducted dissolution of only the test product in distilled water as the medium. The firm should provided comparative individual dissolution data, mean, CV% and the range (highest, lowest) for the test and the reference product. For apparatus 2 rotation speed of either 50 or 75 rpm should be used. Dissolution tests conducted with 100 rpm is not acceptable.

4. The pharmacokinetic parameters for the test and reference products were comparable. The ratios of the test mean to the reference mean are within $\pm 20\%$.
5. The firm has also collected pharmacodynamic data, heart rate, diastolic and systolic blood pressure for each time point. The pharmacodynamic parameter profiles for test and reference are similar.
6. No serious adverse events reported. Majority of the adverse events reported was for headaches. This is not uncommon for nitrates which cause vasodilatation.
7. Assay method validation data for the Pre-study and within-study are acceptable.
8. The theoretical batch size of the test product is tablets.
9. At present, a compendial dissolution method is not available for this product.

IX. Deficiency:

1. Dissolution Testing

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested *in vivo*.

The firm has conducted dissolution of only the test product in distilled water as the medium. The firm has not provided comparative dissolution with the reference product and individual dissolution data, mean, CV% and range for the test and the reference product. For apparatus 2 rotation speed of either 50 or 75 rpm should be used. Dissolution tests conducted with 100 rpm is not acceptable.

The firm has provided comparative dissolution data of test and reference product in buffered media of pH 1.2 - 7.2 using USP apparatus II, 900 ml of media and rotation speed of 100 rpm.

Method of Dissolution testing as specified in Guidance for In-Vitro Dissolution testing for extended release formulation is shown below. General conditions are as follows:

Apparatus:	USP 23 Apparatus 2 (paddle)
RPM:	50 or 75 rpm
Medium:	aqueous buffered media of various pH
Volume:	900 mL
Sampling Times:	1, 2, and 4 hours, and every two hours until 80% of the drug is released
Tolerance (Q):	As established
Analytical:	As per USP 23, if available, or other validated method

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The

mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Please note for a scored tablet, dissolution test for half-tablet testing is required. Twelve (12) tablets should be broken, and each half of each tablet should be tested so that 12 separate units are tested for test and reference product. Testing should not be conducted by breaking 6 tablets into 12 halves and testing the 12 halves, i.e., each half tested should come from a separate tablet.

2. The graphs of dissolution profile shows an incorrect x-axis scale (no break in the axis) and instead of a 22 hour data point 24 hour data point is plotted, needs clarification.

In future, for ease of review it would be helpful if all dissolution related information is placed under the heading of comparative dissolution.

TABLE I

LOT NO:50CO2A(EI.AN,S 60mg ER Tablet)

pit of medium	Hour %RELEASE	1	2	3	4	5	6	7	8	9	10	11	12	Mean	CV	RANGE
12	1													26.33	4.1	23.61- 27.36
	2													38.59	3.1	35.18- 39.90
	4													56.27	2.8	51.73- 57.70
	6													70.11	2.8	64.30- 72.15
	8													80.81	3.2	74.14- 83.94
	10													88.43	2.8	81.29- 90.79
	22												102.33	2.1	98.03-105.79	
40	1													25.22	3.4	23.32- 26.32
	2													36.20	3.8	33.08- 38.94
	4													53.65	4.2	47.50- 57.03
	6													65.79	4.6	57.61- 69.69
	8													75.79	4.6	66.71- 80.88
	10													83.24	4.1	74.31- 88.67
	22												103.17	2.8	97.76-107.94	
62	1													25.30	3.7	23.02- 26.15
	2													36.63	4.6	33.05- 38.61
	4													54.48	5.1	49.03- 56.78
	6													67.22	5.3	61.14- 70.89
	8													78.19	5.2	70.63- 82.22
	10													86.16	4.9	79.11- 90.38
	22												103.52	2.6	98.02-107.78	
72	1													25.71	3.1	24.60- 26.90
	2													36.98	3.2	34.94- 38.83
	4													54.75	3.6	51.50- 57.47
	6													68.08	4.1	63.73- 71.51
	8													78.09	4.1	71.63- 81.72
	10													84.61	3.8	78.88- 89.42
	22												103.51	2.5	99.77-109.02	

000005 00177

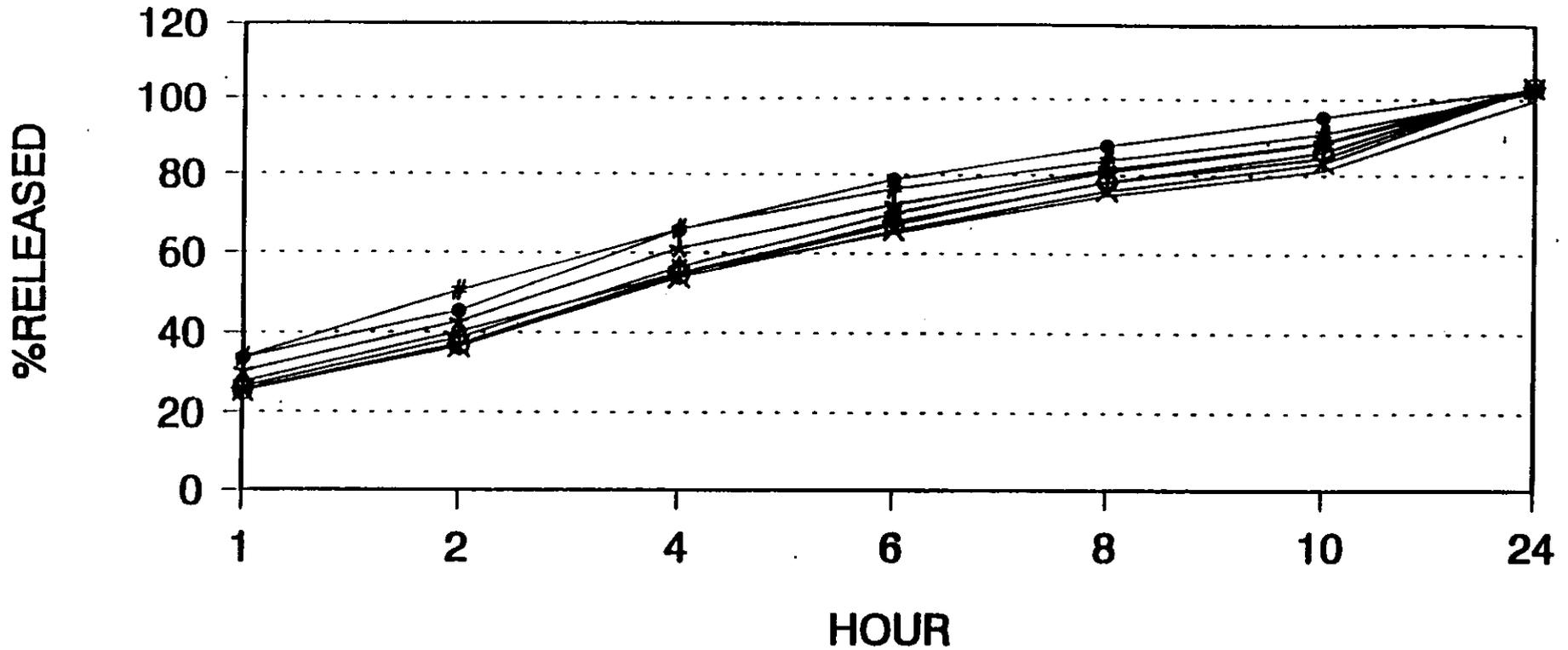
TABLE 2

LOT NO: 5DJC-1 (IMDUR 60mg Isosorbide-5 mononitrate)

pill of medium	Hour % RELEASE	1	2	3	4	5	6	7	8	9	10	11	12	Mean	CV	RANGE
12	1													33.72	2.2	32.26 - 34.99
	2													50.17	1.6	48.96 - 51.53
	4													65.03	2.3	64.04 - 69.19
	6													76.23	2.5	72.25 - 80.05
	8												14	83.96	2.8	81.02 - 88.77
	10												01	90.91	1.9	88.87 - 95.05
	22												5	101.92	1.7	99.81 - 104.75
40	1													27.60	2.6	26.32 - 29.18
	2													40.07	1.8	38.86 - 41.14
	4													54.78	1.6	53.46 - 56.26
	6													65.19	1.6	63.90 - 67.86
	8												13	74.58	1.6	72.09 - 76.33
	10												0	81.26	1.7	79.34 - 83.92
	22												0.65	99.79	1.8	96.90 - 103.91
62	1												3.36	33.58	3.0	32.31 - 35.31
	2													45.04	2.5	43.51 - 46.73
	4													65.72	2.7	63.77 - 69.91
	6													78.70	2.9	76.40 - 84.88
	8													87.72	1.0	86.60 - 89.28
	10													95.30	1.1	93.92 - 97.68
	22												102.92	2.0	99.10 - 106.22	
72	1													30.21	4.6	28.43 - 33.93
	2													47.55	2.2	40.78 - 43.89
	4													61.09	1.8	59.28 - 62.72
	6													72.31	1.6	70.20 - 73.74
	8													81.50	2.2	79.35 - 85.24
	10													88.67	1.8	86.72 - 91.21
	22												103.39	1.4	101.26 - 105.39	

000005 090173

Dissolution profile of Imdur 60mg tablets and Elan's 60mg ER Tablets in medium at different pH's



ELAN1.2 # IMDUR1.2 × ELAN4.0 — IMDUR4.0
○ ELAN6.2 ● IMDUR6.2 + ELAN7.2 * IMDUR7.2

000181

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-041

APPLICANT: Elan Corporation

DRUG PRODUCT: Isosorbide Mononitrate Extended Release Tablets,
60 mg

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

1. Dissolution Testing

Dissolution testing should be conducted on 12 dosage units of the test product versus 12 units of the reference product. The biostudy lots should be used for those product strengths tested *in vivo*.

You conducted dissolution on only the test product in distilled water as the medium. You did not provide comparative dissolution with the reference product and individual dissolution data, mean, CV% and range for the test and the reference product.

You provided comparative dissolution data of test and reference product in buffered media of pH 1.2 - 7.2 using U.S.P. apparatus II, 900 ml of media and rotation speed of rpm. Dissolution tests conducted with rpm are not acceptable. Apparatus 2 with rotation speed of either 50 or 75 rpm should be used.

Method of Dissolution testing as specified in Guidance for In-Vitro Dissolution testing for extended release formulation is shown below.

General conditions are as follows:

Apparatus:	USP 23 Apparatus 2 (paddle)
RPM:	50 or 75 rpm
Medium:	aqueous buffered media of various pH*
Volume:	900 mL
Sampling Times:	1, 2, and 4 hours, and every two hours until 80% of the drug is released
Tolerance (Q):	As established
Analytical:	As per USP 23, if available, or other validated method

* Dissolution should be conducted in buffered media with pH of 1.2, 4.2, 6.2 and 7.2, buffered media are to be prepared as per USP23, pp2049 - 2050.

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Please note that for a scored tablet, a dissolution test for half-tablet testing is required. Twelve (12) tablets should be broken, and each half of each tablet should be tested so that 12 separate units are tested for test and reference product. Testing should not be conducted by breaking 6 tablets into 12 halves and testing the 12 halves, i.e., each half tested should come from a separate tablet.

2. The graphs of dissolution profile showed an incorrect x-axis scale (no break in the axis) and instead of a 22 hour data point 24 hour data point is plotted. Please provide clarification.

In the future, for ease of review it would be helpful if all dissolution related information were placed under the heading of comparative dissolution.

Sincerely yours,



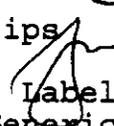
Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Should you have questions concerning this application, contact:

Tim Ames

Project Manager
(301) 594-0305

Sincerely yours,

Jerry Phillips  2/24/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



502(f)(2)(B) 12
- 7/22/96
2/17/97

December 31, 1996

Mr. Douglas Sporn
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: Isosorbide Mononitrate Extended Extended-Release Tablets 60 mg
Original ANDA Submission**

Dear Mr. Sporn:

Élan Pharmaceutical Research Corporation is enclosing herein an original Abbreviated New Drug Application (ANDA) for a 60 mg Isosorbide Mononitrate Extended-Release Tablet that is bioequivalent to the listed drug, IMDUR®, manufactured by Schering Plough (Key Pharmaceuticals) pursuant to NDA 12,940. This application is being submitted on behalf of Élan Corporation, plc of Athlone, Ireland.

This ANDA consists of twelve volumes. The archival copy (blue jacket) contains all the information required in the ANDA and a technical review copy (red jacket) which contains all of the information in the archival copy with the exception of the Bioequivalence section (VI). The Bioequivalence section (VI) is provided in orange jackets. Additional copies (4) of the Methods Validation Package are also included and identified accordingly.

Furthermore, this letter certifies that concurrent with the filing of this ANDA, a true Field Inspection Copy of the chemistry/technical section of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is included with the submission to be held at the Agency's Documentation Management Branch until requested. The manufacture of Isosorbide Mononitrate Extended Release Tablets will be at Élan's Athlone, Ireland facility.

DEC 31 1996

élan pharmaceutical research corp.

1300 Gould Drive, Gainesville, Georgia 30504-3947, USA
Telephone: (770) 534-8239, Fax: (770) 534-8247



Please direct any written communications regarding this ANDA to the undersigned or Helan Ryan at the above address. If you need to call or fax me, my numbers are (770) 534-8239 (phone) and (770) 531-0835 (fax).

Sincerely yours,

Roger Wayne Wiley, R. Ph.
Director, North America Regulatory Affairs

K:\ismn60\fdal231\hr/hr