

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75041

CORRESPONDENCE



élan pharmaceutical research corp.

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June 2, 1997

Ms. Lizzie Sanchez
Consumer Safety Officer
Division of Bioequivalence
OGD, CDER, FDA, Room E 130
7500 Standish Place
Metro Park North
Rockville, MD 20855

RE: ANDA 75-041 Isosorbide Mononitrate 60 mg Tablets

Dear Ms. Sanchez:

Reference is made to our Abbreviated New Drug Application for Isosorbide Mononitrate Extended Release Tablets 60 mg (ANDA 75-041). In addition, reference is made to your telephone request (on 5-29-97) for supplementary information for use in review of the bioequivalence studies.

In response to your telephone call, please note the following:

Comment 1: *Please supply Assay and Content Uniformity data for test and reference drug products.*

Response: In accordance with the Guidance for *In Vitro* Dissolution Testing prepared by the Division of Bioequivalence in the Office of Generic Drugs, the dissolution profiles of the Test (Élan) and Reference (IMDUR™) products were compared.

Dissolution, assay and content of uniformity for the test batch are provided on the Certificate of Analysis for Lot #50C02A, which is located in Volume 3, of the original ANDA submission (page 211). Identity, dissolution and assay results are provided for the reference IMDUR™. For ease of review, Certificate of Analyses for both test (Lot #50C02A) and reference (Lot #5-DJC-1) are provided in Attachment A.

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Comment 2: *Please supply the formulation of the test product (Élan) in a tabular format.*

Response: The formulation of the test product, Isosorbide Mononitrate Extended Release Tablets 60 mg, is provided in Volume 2, Pages 3 and 4 of the original ANDA. A copy of these pages are provided in Attachment B.

Comment 3: *Comparative Dissolution: Present individual data, means and ranges for test and reference products.*

Response: The information requested is provided in Volume 1, Section 6, Pages 172 (Test Product) and 173 (Reference Product) of the original ANDA. For ease of review copies of these pages with the addition of data on ranges are provided in Attachment C.

Comment 4: *Dissolution Testing: Protocol provides for data at 0.5, 2, 4, 6 and 12 hours. Data presented in the ANDA is for 0.5, 2, 4, 6, 10 and 22 hours. Reviewer has requested data as proposed in the protocol.*

Response: Analytical testing of the Élan (test) formulation of Isosorbide Mononitrate 60 mg Extended-release Tablets was in accordance with the analytical protocol (XFT 10011/Revision 2), which was provided in the original ANDA, Volume 1, Page 125 and Volume 3, Page 197.

Dissolution testing time points of 0.5, 2.0, 4.0, 6.0, 10.0 and 22.0 hours were applied to the test batch. For ease of review, a copy of this analytical protocol (XFT 10011/Rev. 2) and the accompanying Certificate of Analysis for the test batch (Lot #50C02A) is provided in Attachment D.

Based on the results of the pivotal bioequivalence studies and accompanying dissolution testing, revised dissolution time points of 0.5, 2, 4, 6 and 12 hours were recommended as suitable for monitoring *in-vitro* drug release. Therefore, a second protocol (PFT 75574/Original) "proposed for scale-up," was also provided in the ANDA.

This revised "proposed for scale up" protocol was provided in Volume 3 on Page 213 of the original ANDA. For ease of review, a copy of this document is provided in Attachment E.



A paper copy of this communication is being submitted to the application via the mail.

Should you have any further questions, please contact the undersigned or Helen Ryan at (770) 534-8239.

Sincerely,

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



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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: 75-041: ISOSORBIDE MONONITRATE Extended-Release Tablets 60 mg.
Response to Chemistry and Labeling Deficiencies**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for ISOSORBIDE MONONITRATE Extended-release Tablets 60 mg (ANDA 75-041) dated December 31, 1996. In addition, reference is also made to the deficiency letters for chemistry and labeling dated August 6, 1997. A copy of this letter is provided in Attachment 1. We have responded to each of the chemistry deficiencies cited in the aforementioned letter in a question/answer format with FDA questions in bold and Elan's responses in standard type.

In response to the attached labeling deficiencies, twelve copies of final printed labels and labeling for the drug product are provided in Attachment 16. In addition, a side-by-side comparison of the original Elan labeling compared to the revised labeling including the agencies recommendations is also provided as requested in Attachment 17. Also, please note that the trade name Nitroprn® SR has now been added to the labeling.

We also acknowledge comments B.1. and B.2. at the close of your August 6, 1997 correspondence regarding the DMF holder and the request for an updated stability report. In regards to the request for additional stability data, we have provided an updated report through 18 months at controlled room temperature in Attachment 13.

Please direct any written communications regarding this ANDA to the undersigned or Helen 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,


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

Enclosures

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Labeling, version directed
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élan pharmaceutical research corp.

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April 16, 1998

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

SP
AM

**RE: MINOR AMENDMENT: ANDA 75-041: Isosorbide Mononitrate
Extended-release Tablets, 60 mg -Response to CMC /Labeling Deficiency
Telefax of 3/27/98**

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. In addition, reference is made to the MINOR DEFICIENCY chemistry manufacturing & controls (CMC) and labeling deficiency letter telefaxed to Elan on March 27, 1998. Copies of the telefaxes are provided in Attachment 1.

We have responded to each of the chemistry and labeling deficiencies cited in the aforementioned telefax in a question/answer format with FDA questions in bold and Elan's responses in standard type. Please note that, in addition to responding to the CMC and labeling deficiencies, twelve sets of final printed labeling (container labels for 100's & 500's and package inserts) are provided in the red (CMC) jacket and six sets of final printed labeling are provided in the blue (archives) jacket. In addition, a side-by-side comparison of the previous version of Elan's labeling compared to the enclosed revised labeling is also provided (Attachment 7).

Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. Please feel free to call or fax me at 770-534-8239 (phone) and 770 531-0835 (fax).

Sincerely,

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

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Handwritten signature
4/28/98



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VIA TELEFAX (301) 443-3839

ORIG AMENDMENT

May 8, 1998

11/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

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**RE: MINOR TELEPHONE AMENDMENT: ANDA 75-041; Isosorbide Mononitrate
Extended-release Tablets 60 mg -Response to Chemistry and Labeling Deficiencies**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for ISOSORBIDE MONONITRATE Extended-release Tablets, 60 mg (ANDA 75-041) dated December 31, 1996. In addition, reference is also made to the telefaxed Minor Telephone Amendment deficiency faxed on April 29, 1998. A copy of this telefax is provided in Attachment 1. We have responded to each of the comments cited in the aforementioned telefax in a question/answer format with FDA questions in **bold** and Elan's responses in standard type.

- 1. When statistical evidence shows a blend analysis is no longer necessary, please confirm that you will submit a supplement under 314.70(b)(2) (iv) prior to deleting the test.**

Response:

In accordance with the agency recommendation in the March 26, 1998 Minor CMC deficiency (comment No.3) which recommends the taking of blend samples to provide a good statistical basis for evaluating variability, Elan has conducted blend uniformity testing on ten (10) batches of recently manufactured Isosorbide Mononitrate Extended Release Tablets 60mg. Results of this unit dose sampling from each of the ten batches (10 samples/batch x 10 batches = 100 samples) are provided in Attachment 2 of this submission.

Review of these data confirms that the process is producing blends that are within the range of potency with a variability (RSD) that is less than the 5% RSD proposed by the agency in the current Telephone Amendment (comment No.2). On the basis of these results Elan proposes to discontinue this labor intensive sampling and analytical testing activity and return to composite blend sampling as an in-process control.

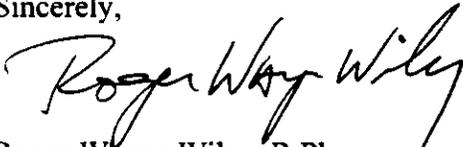
2. **Originally you indicated that your acceptance criterion for the blend analysis was of label claim. In your amendment dated April 16, 1998 you further clarify that the mean assay value must be between but all individual values must be between with an RSD of NMT. In essence you are using content uniformity criteria for the blend. We feel these criteria are inappropriate, and that each individual sample should at least meet compendial assay limits of 90-110%. In addition, we feel an RSD of 4-5% is a more appropriate limit on variation in the blend. Please reconsider your proposed criteria.**

Response:

Post review of the aforementioned unit dose data (Attachment 2) we agree with the agency's proposal that each individual sample (unit dose or composite) meet the assay limits of 90-110% with an RSD of not greater than 5% for variation in the blend.

Please direct any written communications regarding this ANDA to the undersigned or Sharon Hamm at the above address. Please feel free to call or fax me at 770-534-8239 (phone) and 770 531-0835 (fax).

Sincerely,



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