

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75041

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

<p>Wayne (Roger) Wiley called last Friday (3-27-98) asking for clarification of a labeling comment in the fax that we sent to Elan 3-26-98. Specifically concerning the storage temperature recommendation. The RLD for Isosorbide Mononitrate has 2°-30°C while Elan proposed CRT 20°C-25°C. After discussion with J. Harrison, S. Rosencrance, C. Hoppes and myself it was decided that we would ask the firm to change to 2°-30°C to be the same as the innovator. J. Harrison stated that if the firm has conducted accelerated stability testing under high humidity above CRT (they have) and if the container lid provides a tight seal (it does) and if the drug product comes with a desiccant (it does) and if the company has demonstrated that the drug product is stable at CRT (they have) then we can allow the expanded storage range of 2°-30°C. I called Mr. Wiley back today and told him they could use the storage range 2°-30°C on their labels and labeling.</p>	<p>DATE March 30, 1998</p>
	<p>ANDA NUMBER 75-041</p>
	<p>IND NUMBER</p>
	<p align="center">TELECON</p>
	<p>INITIATED BY MADE <input checked="" type="checkbox"/> APPLICANT/ <input checked="" type="checkbox"/> BY SPONSOR TELE.</p> <p>FDA — IN PERSON</p>
	<p>PRODUCT NAME Isosorbide Mononitrate</p>
	<p>FIRM NAME Elan Pharmaceuticals</p>
	<p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Wayne (Roger) Wiley Reg. Affairs</p>
	<p>TELEPHONE NUMBER (770) 538-6360</p>
	<p>SIGNATURE Adolph Veza <i>Adolph Veza 3/30/98</i></p>

Division of Labeling and Program Support

"First Generic"
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: -75-041

Date of Submission: December 31, 1996

Applicant's Name: Elan Pharmaceutical Research Corporation

Established Name: Isosorbide Mononitrate Extended-release
Tablets, 60 mg

Labeling Deficiencies:

1. CONTAINER: 100s and 500s
 - a. The established name should appear with a hyphen and a lowercase "r" for Release:

Isosorbide Mononitrate Extended-release
Tablets
 - b. Place a space between "60" and "mg".
 - c. A period should follow the Usual Dosage Statement.
 - d. Your manufactured for/by statement on your labels and labeling for your USA and foreign company must comply with 21 CFR 201.1(6)(i). The place of business shall include the street address, city, state/country and zip code/ mailing code. Please see the citation above for guidance.
2. INSERT
 - a. GENERAL COMMENT

Your section and subsection headings should be distinguishable from the running text. Please place a hyphen or a colon after your headings.
 - b. TITLE - The established name should appear with a hyphen and a lowercase 'r' for Release. Revise throughout the insert.

Isosorbide Mononitrate Extended-release Tablets,
60 mg

c. DESCRIPTION

- i. Please include the molecular formula and molecular weight.
- ii. "Lactose monohydrate" rather than "monohydratelactose".
- iii. Delete "(ER)" from the second paragraph.

d. CLINICAL PHARMACOLOGY

- i. Use "Extended-release" rather than "ER". Revise throughout the insert.
- ii. Pharmacokinetics and Metabolism, fourth paragraph ... i.e., ... (insert the two periods).
- iii. Clinical Trials - ..."1 to 3-week"... (delete the first hyphen).

e. PRECAUTIONS - Pediatric Use

...ISMN in pediatric patients have...

f. ADVERSE REACTIONS

Add the following as the last paragraph:

In addition, the following spontaneous adverse event has been reported during the marketing of isosorbide mononitrate: syncope.

g. OVERDOSAGE

i. Hemodynamic Effects

(A) Delete the extra line space that follows the second paragraph.

(B) ...(e.g.,...) [add the two periods].

- ii. Methemoglobinemia - First paragraph, last sentence - Use "7.8 to 11.1" rather than "7.8-11.1" mg.

Please revise your labels and labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

J /S/ *'*
Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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,

/s/

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

BIOEQUIVALENCY - DEFICIENCIES

175-041 *Isorhale-S-Monontrate*
(Elian) 60mg/2 tablet

2-31-97

FASTING STUDY (STF)

Clinical: _____
Analytical: _____

Strengths: 60mg

Outcome: ~~AC~~ **IC** UN NC *incomplete due to dis*

2-31-96

2. FOOD STUDY (STP)

Clinical: _____
Analytical: _____

Strengths: 60mg

Outcome: ~~AC~~ **IC** UN NC

2-31-96

3. MULTIPLE DOSE STUDY (STM)

Clinical: _____
Analytical: _____

Strengths: 60mg

Outcome: ~~AC~~ **IC** UN NC

4. DISSOLUTION DATA (DIS)

All Strengths

Outcome: AC IC UN NC

2-9-97 (5)

5. STUDY AMENDMENT (STA)

Strengths: telephone amendment

Outcome: AC IC UN NC

6. WAIVER (WAI)

Strengths: _____

Outcome: AC IC UN NC

7. DISSOLUTION WAIVER (DIW)

Strengths: _____

Outcome: AC IC UN NC

3-10-97 (8)

8. OTHER (OTH) diskette

Strengths: _____

Outcome: AC IC UN **NC**

9. OTHER OPTIONS (less common):

- a. Protocol (PRO)
- b. Protocol Amendment (PRA)
- c. Protocol/Dissolution (PRD)

- d. Special Dosage (STS)
- e. Study/Dissolution (STD)
- f. Bio study (STU)

Outcome: AC IC UN NC

OUTCOME DECISIONS:

AC - Acceptable
NC - No Action

~~UN - Unacceptable (fatal flaw)~~
IC - Incomplete

Comments:

Incomplete due to dissolution