Labels and labeling satisfactory for approval pending minor drafting labeling 3/26/98 /S/

ABBOTT

Hospital Products Division
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-3500

March 18, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
METRO PARK NORTH II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn, M.D.
Director

Facsimilie Amendment

Re: ANDA 74-941 Diltiazem Hydrochloride Injection, 5 mg/mL (Vials)

Abbott Laboratories hereby submits additional information as requested in the Agency's facsimilie deficiency letter dated February 27, 1998. The letter requests additional information pertaining to Labeling for the above named ANDA. Additionally, please provide a side by side comparison of these changes with differences annotated.

Labeling Deficiencies:

Request 1: Container (5mL and 10 mL vials)

...At the time of the next printing replace the " Caution: Federal Law..." statement with " Rx only". See Section 126 of the FDA Modernization Act of 1997.

Response 1: Acknowledged. Appended in Exhibit I is Diltiazem 5mg/mL, 5mL and 10mL vial container labeling incorporating this statement.

Request 3: Carton (10x5 mL and 10x10 mL)

See comment above.

Response 3: Acknowledged. Appended in Exhibit II is Diltiazem 5mg/mL 5mL and 10mL carton labeling incorporating this statement.

Request 4: **Insert**

a. CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism, last paragraph: Bold "oral" in the first sentence.

b. PRECAUTIONS

Beta-blockers, first sentence – Revise to read "on" rather than "receiving"

c. ADVERSE REACTIONS

Other, paragraph two – Italicize and bold "oral".

d. HOW SUPPLIED

Replace the " Caution: Federal Law..." statement with " Rx only". See Section 126 of the FDA Modernization Act of 1997.

Response 4: **a-d**

Acknowledged. Appended in Exhibit III is the package insert for Diltiazem 5mg/mL, 5mL and 10mL vials incorporating the requested changes.

We trust this information is correct.

Sincerely,

Abbott Laboratories

Thomas P. Sampogna

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3-98fda

ABBOTT

Hospital Products Division

Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-3500

January 22, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
METRO PARK NORTH II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn, M.D.
Director

Facsimilie Amendment

Re: ANDA 74-941 Diltiazem Hydrochloride Injection, 5 mg/mL (Vials)

Abbott Laboratories hereby submits additional information as requested in the Agency's facsimilie deficiency letter dated December 22, 1997. The letter requests information pertaining to Chemistry, Labeling and Microbiology for the above named ANDA.

A. Chemistry Deficiencies

Labeling Deficiencies (continued)

Request 1b: **We note that this ANDA shares an insert with ANDA Please note that if both products are not approved at the same time you will be asked to revise your labeling accordingly.**

Response 1b: Acknowledged. We have removed the reference to ANDA from the ANDA 74-941 insert.

2. Container **(5mL and 10mL vials)**

We acknowledge your statement regarding your failure to include some of the requested statements due to space constraints.

Request 2b: **Revise the expressions of strength to read as follows:**

___mg/___mL or ___mg/___mL (5mg/mL)
(5mg/mL)

Response 2b: Agreed. The expression of strength will now read

___mg/___mL (5mg/mL)

Appended in Exhibit II is final printed labeing for the 5mL and 10mL vial container configuartions reflecting this revision.

3. Carton **(10 x 5mL and 10 x 10mL)**

We acknowledge your comments regarding citric acid USP.

Request 3b: **See comment 2(b) above under CONTAINER.**

Response3b: Agreed. The expression of strength will now read

___mg/___mL (5mg/mL)

Appended in Exhibit III is final printed labeing for the 5mL and 10mL vial carton configurations reflecting this revision.

Labeling Deficiencies (continued)

4. Insert

a. DESCRIPTION

Request 4ai: **Revise the chemical name to read:**

(+) -5- [2- (Dimethylamino) ethyl] -cis-2,3-dihydro-3-hydroxy-2- (p-methoxyphenyl) -1,5-benzothiazepin-4 (5H) -one acetate (ester) monohydrochloride.

Response 4ai: Acknowledged. The chemical name has been revised to read:

(+) -5- [2- (Dimethylamino) ethyl] -cis-2,3-dihydro-3-hydroxy-2- (p-methoxyphenyl) -1,5-benzothiazepin-4 (5H) -one acetate (ester) monohydrochloride.

Appended in Exhibit IV is a copy of the package insert reflecting this change.

Request 4aii: **See 1(a) GENERAL COMMENTS above.**

Response 4aii: Acknowledged. The statement "sodium hydroxide or hydroclonc acid" will be revised to read "sodium hydroxide **and/or** hydrochloric acid". Please see Exhibit IV.

b. HOW SUPPLIED

Request4i: **Please indicate your carton configuration in this section.**

Response4i: Acknowledged. Please see Exhibit IV for this information.

Request4ii: **Include the strength (mg/mL) with the established name in this section.**

Response 4ii: Acknowledged. Please see Exhibit IV for this information.

Labeling Deficiencies (continued)

Request 4iii: **We encourage the use of the NDC number in this section.**

Response 4iii: Abbott Laboratories markets many thousands of products and has tried to develop a standard labeling format and nomenclature. NDC identification numbers were reviewed for inclusion in the HOW SUPPLIED section of all inserts. Abbott Laboratories has standardized all of its package insert information to include the product list (catalog) numbers in this description. In order to mainitain this standardized nomenclature, we have maintained the list number format on this insert.

Request 4iv: **We note that you have included 30mL and 50mL syringes in this section. We have no record of any submission for these sizes. Please comment.**

Response 4iv: Acknowledged. There is no submission for a syringe. These sizes were considered for a submission based on an approved suitability petition from another company. However. an internal decision was made not make a formal submission for these sizes.

C. Microbiology Deficiencies

Request 1: **Please clarify the statement regarding bioburden testing. It appears that there is bioburden testing performed; however, the frequency of testing is not clear. You should be testing each commercial batch to determine the bioburden of the subject drug product solution prior to filtration. This is an filled product and decisions regarding the reduction in testing for bioburden should be based on historical data, i.e., after several commercial lots."**

Response 1: For new and unapproved drug product, routine bioburden testing is performed on each production batch of ıg product prior to However, for commercially approved drug product, routine bioburden testing is performed on a minimum of once per month per product concentration. The frequency of once per month is based on acceptable review of drug product holding time validation, filter validation and routine bioburden data obtained on previous production batches manufactured.

Microbiology Deficiencies (continued)

In addition, based upon the Agency's recommendation, we hereby commit to perform testing for bioburden on the first three commercial batches of Diltiazem Hydrochloride Injection (5 mg/mL). The bioburden testing frequency of once per month for Diltiazem Hydrochloride Injection (5 mg/mL) will be based upon acceptable review of the historical bioburden data obtained on previous production batches manufactured (including the first three commercial batches), holding time validation and filter validation.

We trust this information is correct.

Sincerely,

Abbott Laboratories

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ABBOTT

Hospital Products Division

Abbott Laboratories
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ORIG AMENDMENT

October 7, 1997

N/AM

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
METRO PARK NORTH II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Label review
dropped 10/23/97
A. Vass

ATTENTION: Douglas Sporn, M.D.
Director

Minor Amendment

Re: ANDA 74-941 Diltiazem Hydrochloride Injection, 5 mg/mL (Vials)

Abbott Laboratories acquired the injectable drug division from Sanofi Winthrop Pharmaceuticals, New York, N.Y., 10016, in July of 1997. We are now the sponsor of numerous ANDA's in addition to 74-941. We hereby submit additional information as requested in the Agency's deficiency letter dated May 14, 1997. The letter requests information pertaining to Microbiology, Chemistry and Labeling for the above named ANDA. A copy of the letter is attached in Exhibit I for your review.

A. Microbiology Deficiencies:

Page(s) 4

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

We note and acknowledge that satisfactory methods validation must be performed on the finished product by an FDA laboratory prior to the approval of this ANDA.

C. Labeling Deficiencies
General Comment

We hereby submit corrected labeling for the carton, container and package insert. The information submitted is a comparison to the innovator (Hoescht Marion Roussel) and attached in Exhibit XI. As mentioned in paragraph 1 of this communication we are now the sponsor of this application from Sanofi / Winthrop and have incorporated our labeling into this submission. All corrections have been implemented with the exception of the following requests.

Request 1: We note that in the description of your product's manufacturing and processing instructions appearing on page 208 of this application, that the sodium hydroxide and/or hydrochloric acid are added to adjust pH. Your carton and insert labeling, however, state that sodium hydroxide or hydrochloric acid are used to adjust pH. Please revise and/or comment.

Response 1: The description of the sodium hydroxide or hydrochloric acid is consistent with the innovator labeling of the same two ingredients.

CONTAINER (5mL and 10mL)

Request 2e: Insert the following text to appear in conjunction with temperature storage recommendations:

DO NOT FREEZE. May be stored at room temperature for up to one month. Destroy ater 1 month at room temperature.

Response 2e: The placement of this statement is consistent with the innovator and prominently displayed on the carton. Additionally, the containers include the statement and space to notate:
Date Removed From Refrigerator_____ and Date to Be Discarded_____. The size constraints of the container label prohibit the addition of the requested statements.