

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74941

BIOEQUIVALENCE REVIEW(S)

ANDA 74-941

Sanofi Winthrop, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Avenue
New York NY 10016-1389

JAN 23 1987



Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Injection, 5 mg/mL, 5 mL and 10 mL vials.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

A stylized handwritten signature in black ink, appearing to read 'R/P'.

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 17 1997

Diltiazem Hydrochloride Injection
5 mg/mL; 5 mL and 10 mL Vials
ANDA #74-941
Reviewer: Moheb H. Makary
WP. 74941W.896

Review of a Waiver Request

I. Objective:

The firm has requested a waiver of bioequivalence study requirements for its product Diltiazem Hydrochloride Injection, 5 mg/mL; 5 mL and 10 mL Vials. Innovator product is Cardizem[®] Injectable 5 mg/mL; 5 mL and 10 mL Vials, manufactured by Hoechst Marion Roussel. Diltiazem Hydrochloride Injection is indicated for atrial fibrillation and paroxysmal supraventricular tachycardia. It is a clear, colorless, sterile, nonpyrogenic solution with a pH range of

II. Formulation Comparison: (Not to be released under FOI)

Diltiazem Hydrochloride Injection, 5 mg/mL; 5 mL and 10 mL Vials

	Test Product <u>Per mL</u>	Reference Product <u>Per mL</u>
<u>Ingredients</u>		
Diltiazem Hydrochloride, USP	5 mg	5 mg
Citric Acid	0.75 mg	---
Citric Acid, USP*	---	0.75 mg
Sodium Citrate dihydrate, USP	0.65 mg	0.65 mg
Sorbitol Solution, USP	71.4 mg	71.4 mg
Sodium Hydroxide, or Hydrochloric Acid, USP	for pH adjustment () for pH adjustment	
Water for Injection, USP	qs to 1 mL	qs to 1 mL

* The total citrate concentration in the reference listed drug (Cardizem[®]) was analyzed by ion-pair chromatography to determine if the amount of citric acid is the anhydrous or monohydrate form. The study confirmed that 0.75 mg per mL of monohydrate citric acid is used in the reference listed drug formulation.

Comments:

1. The active and inactive ingredients and their concentrations for the test product are the same as those of the innovator's Cardizem[®] Injectable 5 mg/mL; 5 mL and 10 mL Vials, manufactured

by Hoechst Marion Roussel.

2. Waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22(b)(1).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Sanofi Winthrop, Inc., demonstrates that Diltiazem Hydrochloride for Injection, 5 mg/mL; 5 mL and 10 mL Vials falls under 21 CFR 320.22 (b)(1). The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Cardizem® Injectable 5 mg/mL; 5 mL and 10 mL Vials, manufactured by Hoechst Marion Merrell Roussel.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/

Date: 1/16/97

Concur: ^ /S/
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date: 1/17/97

MMakary/1-14-97 wp 74941W.896

, Division

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74941

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 74-941

G PRODUCT: Diltiazem Hydrochloride Injection

FIRM: Abbott

DOSAGE FORM: SVP (Injection)

STRENGTH: 5 mg/mL

CGMP STATEMENT: Included in original submission - p. 190

EIR STATUS UPDATE: Satisfactory 3/26/97

BIO STUDY: Waiver of study requirements granted 1/17/97.

VALIDATION: Methods validation performed by FDA Denver District Laboratory. The laboratory comments were satisfactorily addressed by the applicant.

STABILITY: Stability is satisfactory. Testing and specifications are:

Description: Clear, colorless solution

pH:

Assay: 90.0% - 110.0%

Desacetyl Diltiazem HCl:

Degradation Products: Individ.

Particulate Matter: Meets USP 23 <781>

Sterility: Meets USP 23 <71>

BET: USP 23 <85>: EU/mL

Sterility is tested initially, annually and at expiration.

BET is tested initially and at expiration.

LABELING: Satisfactory

Container label: satisfactory, A. Vezza, HFD-613, 3/26/98

Insert label: satisfactory, A. Vezza, HFD-613, 3/26/98

STERILIZATION VALIDATION: Satisfactory 2/6/98, A. High,

SIZE OF BIO BATCH: Lot PD5-083 5 mg/mL in 5 mL vials:
Lot PD5-084 5 mg/mL in 10 mL vials:

SIZE OF STABILITY BATCHES: Same as noted above for bio batch size.

ANDA 74-941

PROPOSED PRODUCTION BATCH: 700L

CHEMIST: Doñald Shōstak ^{3/26/98}

DATE: 1/28/98

TEAM LEADER: Ubrani Venkataramu ^{~ 3/24/98}

DATE: 1/24/98

x:\new\firmam\abbott\ltrs@rev\74941n03.sum

FT by: MAnderson/3/26/98

APPROVAL SUMMARY

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 74-941 Date of Submission: October 7, 1997

Applicant's Name: Abbott Laboratories

Established Name: Diltiazem Hydrochloride Injection

Labeling Deficiencies:

1. GENERAL COMMENTS

- a. We acknowledge your comment that you are following the lead of the innovator when stating the presence of the pH adjustors. However, your manufacturing and processing instructions clearly indicate that sodium hydroxide, hydrochloric acid or both of them may be used in the manufacturing of this drug product. This makes the statement "sodium hydroxide or hydrochloric acid" false and misleading. The correct statement is "sodium hydroxide and/or hydrochloric acid". Please revise.
- b. We note that this ANDA shares an insert with ANDA (syringes). Please note that if both products are not approved at the same time you will be asked to revise your labeling accordingly.

2. CONTAINER (5 mL and 10 mL vials)

- a. We acknowledge your statement regarding your failure to include some of the requested statements due to space constraints.
- b. Revise the expressions of strength to read as follows:

___ mg/___ mL or ___ mg/___ mL (5 mg/mL)
(5 mg/mL)

3. CARTON (10 x 5 mL and 10 x 10 mL)

- a. We acknowledge your comments regarding citric acid USP.

b. See comment 2(b) above under CONTAINER.

4. INSERT

a. DESCRIPTION

i. 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

ii. See 1(a) GENERAL COMMENTS above.

b. HOW SUPPLIED

i. Please indicate your cartoning configuration in this section.

ii. Include the strength (mg/mL) with the established name in this section.

iii. We encourage the use of the NDC number in this section.

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

Please revise your container labels and carton and insert labeling, as instructed above, and submit in final print.

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.

/S/

Jerry Phillips
Director

Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research