

021392_ORIGINAL - APPROVAL - PKG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

21-392

Trade Name: Cardizem LA Extended Release
120-, 180-, 240-, 300-, 360-, and
420 mg Tablets

Generic Name(s): (diltiazem HCl)

Sponsor: Biovail Laboratories, Inc.

Agent:

Approval Date: February 6, 2003

Indication: Provides for the treatment of hypertension

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-392

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	X
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative Document(s)	X
Correspondence	X
Bioresearch Monitoring	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-392

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-392

Biovail Laboratories Incorporated
Attention: John B. Dubeck
c/o Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your new drug application (NDA) dated June 8, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardizem LA (diltiazem hydrochloride) Extended-Release 120, 180, 240, 300, 360 and 420 mg Tablets.

We acknowledge receipt of your submissions dated July 16 and 17, August 1 and 21, September 5, October 8, 22, and 24, November 20 and 22, and December 2, 13, 18 and 30, 2002.

Your submission dated October 24, 2002 constituted a complete response to our June 11, 2002 action letter.

This new drug application provides for the use of Cardizem LA (diltiazem hydrochloride) Extended-Release 120, 180, 240, 300, 360 and 420 mg Tablets for the treatment of hypertension.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the attached draft labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-392." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

The expiration date for Cardizem LA packages in [] bottles and [] blisters will be 18 months.

In addition, we have the following comments and recommendations:

1. We advise you to include females in future bioequivalence studies.
2. A biowaiver is granted for the 120, 180, 240, and 360 mg diltiazem extended-release tablets.
3. You may widen the interim dissolution specification as requested at the 8-hour time point. However, your previously accepted dissolution method of USP Apparatus 2 (paddle) at 100 rpm in 900 mL of pH 5.8 phosphate buffer at 37°C is to remain as previously proposed. The new interim dissolution specifications will be:

TIME (HOURS)	NEW INTERIM DISSOLUTION SPECIFICATIONS
2	NMT
8	
14	
24	NLT

We remind you that future dissolution testing should include timepoints that you have used as well as those listed above. The dissolution timepoints you used for dissolution-stability testing are acceptable on an interim basis pending submission of further stability and lot-release data on the primary stability lots as well as the first three post-marketing production lots as part of the initial Annual Report. Note that final decision specifications will be set at a later time and they will be based on the review of the additional stability and lot release data that the you provide.

NDA 21-392
Page 3

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See attached electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
2/6/03 01:32:28 PM
Signed for Douglas Throckmorton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-392

Approvable Letter (S)



NDA 21-392

Biovail Laboratories Incorporated
Attention: John B. Dubeck
c/o Keller and Heckman
1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your new drug application (NDA) dated June 8, 2001, received June 11, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for diltiazem hydrochloride 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg extended release tablets.

We acknowledge receipt of your submissions dated August 22, October 17, November 2, and December 20, 2001; January 11 and 16, March 8, May 1, 21 and 31, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Please submit a revised debarment statement that complies with the wording specified in section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335a(k)(1)) (Please refer to page 2 of the Draft Guidance for Industry on Submitting Debarment Certification Statements: <http://www.fda.gov/cder/guidance/index.htm>).
2. Lack of bioequivalence data on the 420 mg strength. Additional data are needed for approval of the 420 mg strength in the form of bioequivalence testing against an approved 420 mg sustained release diltiazem (or a combination of two lower strengths of an approved drug).
3. Inadequate timing of dissolution sampling. Your proposed dissolution method [USP Apparatus 2 (paddle), 100 rpm, and 900 ml of phosphate buffer pH 5.8 at 37°C] is acceptable. However, the proposed dissolution sampling time points of 2, 8, 14 and 24 hours are not appropriate. We consider that sampling at 2, 6, 12, and 16 hours will provide more adequate information on the dissolution/release characteristics of your product.

Taking into account that your dissolution-stability data were generated using 2, 8, 14, and 24 hours and submitted in this supplement, your dissolution timepoints are acceptable pending submission of further stability and lot-release data on the primary stability lots as well as the first three post-marketing production lots as a part of your initial Annual Report. This dissolution testing should include testing at the timepoints you have used as well as those listed above (*i.e.*, 2, 6, 8, 12, 14, 16, and 24 hours).

4. Lack of adequate dissolution testing for some of the proposed strengths. The testing listed below is necessary to support the biowaivers, both for approval of the proposed strengths and to support a biowaiver for the proposed manufacturing site changes for the individual strengths of Diltiazem Hydrochloride Extended Release Tablets. Note that this dissolution testing should be conducted at 2, 6, 12 and 16 hours).

- a. For the 300 and 360 mg strengths, you did not perform comparative dissolution studies in 0.1N HCl because you asserted that diltiazem degrades substantially in this medium. We do not accept this, noting that your NDA for diltiazem hydrochloride extended release capsules (NDA 20-939) included dissolution data in this medium. Therefore, before a bio-waiver for the 240 and 300 mg extended release tablets can be granted, you should provide additional dissolution profile comparison data in 0.1N HCl under the same dissolution conditions (i.e., USP Apparatus 2 and 100 rpm).
 - b. For the 120 and 180 mg diltiazem extended release tablets, you should provide dissolution profile comparisons in the application dissolution medium (phosphate buffer pH 5.8) and in the following three dissolution media: 0.1N HCl, buffer pH 4.2, and buffer pH 6.8. The dissolution profiles should be generated using 12 units/lot of the test and reference products and the same dissolution conditions.
5. Inadequate data supporting the marketing of the unscored diltiazem extended release tablets. We note that you used scored extended release tablets to generate all the bioequivalence and dissolution data submitted in this application, but propose to market an unscored tablet form. Before this change may be approved, you should provide additional comparative dissolution profile data in the application dissolution medium (phosphate buffer pH 5.8), showing that this change does not affect your product for each of the proposed strengths.
 6. Inadequate information on the reference standard was submitted. Prior to approval, the following information should be provided: details of characterization, manufacturing process, manufacturer date, lot number, specifications inclusive of tests and test methods, Certificate of Analysis and expiration date.
 7. Inadequate stability data to support your proposed expiration date of 18 months, as your submitted data are based on clinical batches rather than on primary stability data for the application. Your submitted stability data from the primary stability batches are sufficient to support a _____ expiration date for all strengths of diltiazem hydrochloride extended release tablets. Extension of this date will require additional stability testing. Such testing should take into account the changes in the timing of dissolution testing described above.
 8. Inadequate impurity profile comparison data regarding the drug substance from the two proposed manufacturers. A comparison of impurity profiles of all related substances and residual solvents given in the Certificate of Analysis for each supplier and particle size distribution test results of _____ batches of diltiazem hydrochloride from both _____ should be provided. For each comparative test, please use the same test method and analytical instrument. The impurity profile comparison test should not be taken from the batch analyses data provided by the suppliers of drug substance but should be based on the analytical testing that you perform.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert). Corresponding changes should be made to the immediate container and carton labels.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5312

Sincerely,

{See appended electronic signature page}


Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Doug Throckmorton
6/11/02 04:45:33 PM

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling