ANDA 75-116 December 23, 1999

Keller and Heckman
Attention: John Dubeck
U.S. Agent for: Biovail Laboratories, Inc.
1001 G Street, N.W., Suite 500 West
Washington, DC 20001

Dear Sir:

This is in reference to your abbreviated new drug application dated April 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules USP, (Once-a-Day Dosage), 120 mg,
180 mg, 240 mg, and 300 mg.

Reference is also made to our tentative approval letter dated October 22, 1999, and to your amendments dated October 31, 1997; December 30, 1998; and November 19, and December 15, 1999
(2 submissions).

The listed drug product (RLD) referenced in your application, Cardizem CD Capsules of Carderm Capital L.P., is subject to periods of patent protection which will expire on March 26, 2008, (U.S. patent 5,002,776); November 14, 2011 (U.S. patent 5,364,620); August 8, 2012 (U.S. patent 5,439,689); January 16, 2007 (U.S. patent 4,894,240); and May 20, 2011 (U.S. patents 5,470,584 and 5,286,497). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Diltiazem Hydrochloride Extended-release Capsules USP, (Once-a-Day Dosage) will not infringe on any of the listed patents or that the patents are otherwise invalid. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five (45) days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Biovail Laboratories Inc. complied with the requirements of

Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against Biovail Laboratories, Inc. by either the NDA holder (Carderm Capital L.P.) or the patent holder (Elan Corporation PLC) within the statutory forty-five day period. This period elapsed on August 4, 1997.

Please note that the agency was unable to grant final approval to your application upon completion of the scientific review process on October 22, 1999. Instead, the agency issued a tentative approval letter on that date because an abbreviated application for the same drug product containing a Paragraph IV Certification under Section 505(j)(2)(A)(vii)(IV) was previously approved on July 9, 1998 (Cartia XT Capsules of Andrx Corp), thus becoming eligible for 180 days of generic drug exclusivity. We refer you to the agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998) for additional information on this topic. As a result, your application became eligible for final approval beginning 180 days after the first commercial marketing of the drug product under the former application; i.e., December 20, 1999.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diltiazem Hydrochloride Extended-release Capsules USP (Once-a-Day Dosage), 120 mg, 180 mg, 240 mg, and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Cardizem® CD Capsules, 120 mg, 180 mg, 240 mg, and 300 mg, respectively, of Carderm Capital L.P.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution test and tolerances are:

> The dissolution testing should be conducted in 900 mL of water, at 37E C using USP 23 Apparatus I(basket) at 100 rpm. The test product should meet the following specifications:
>
> | | |
> |---|---|
> | 2 hours | [ ] |
> | 8 hours | [ ] |
> | 14 hours | [ ] |
> | 24 hours | [ ] |

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three

production size batches in a supplemental application. A "Special Supplement - Changes Being Effected" (zero) should be submitted when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances a Prior Approval supplement should be submitted.

Under section 506(A) of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research