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**APPLICATION NUMBER:**

**76-151**

**APPROVAL LETTER**

MAY 20 2004

Apotex Corp.  
 Attention: Marcy Macdonald  
 U.S. Agent for: TorPharm Inc.  
 616 Heathrow Drive  
 Lincolnshire, IL 60069

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 29, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Dilt-CD Extended-release Capsules (Diltiazem Hydrochloride Extended-release Capsules USP, 120 mg, 180 mg, 240 mg, and 300 mg (Once-A-Day dosage)).

Reference is also made to your amendments dated October 20, and December 10, 2003; and April 14, 2004.

The listed drug product (RLD) referenced in your application, Cardizem CD Extended-release Capsules of Biovail Laboratories, Inc., is subject to periods of patent protection. The following patents are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, (the "Orange Book"):

<u>U.S. Patent No.</u>	<u>Expiration Date</u>
4,894,240	January 16, 2007
5,470,584	May 20, 2011
5,439,689	August 8, 2012
5,286,497	May 20, 2011
5,364,620	November 14, 2011
5,002,776	March 26, 2008

Note: References to patents will be made by the last three digits of the patent number.

Your application contains paragraph IV patent certifications 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 under this ANDA will not infringe upon the claims of any of the listed patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an infringement action was brought against TorPharm Inc. (TorPharm) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. This action must be brought against TorPharm prior to the expiration of forty-five (45) days from the date the notice provided by TorPharm under paragraph (2)(B)(I) was received by the patent and NDA holder(s).

You have notified the Agency that TorPharm complied with the requirements of Section 505(j)(2)(B) of the Act. As a result, Biovail initiated a lawsuit against you alleging infringement of the '497, '689, and '584 patents in the United States District Court for the Northern District of Illinois, Eastern Division (Biovail Laboratories, Inc. and TWFC, Inc. v. TorPharm Inc., Civil Action No. 01C-9008).

The agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired with respect to the litigation involving the '497, '689, and '584 patents. The agency also recognizes that no legal action regarding the '240, '620, or '776 patents was brought against TorPharm within the statutory forty-five day period.

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 Dilt-CD Extended-release Capsules 120 mg, 180 mg, 240 mg, and 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Cardizem CD Extended-release Capsules, 120 mg, 180 mg, 240 mg, and 300 mg, respectively, of Biovail Laboratories, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution tests and tolerances are:

The dissolution testing should be conducted in 900 mL of 0.1N HCl using USP 24 apparatus II (paddle) at 100 rpm. The test product should meet the following "interim" specifications:

<u>Time</u>	<u>Percent Dissolved</u>
6 hour	_____
12 hours	_____
18 hours	_____
24 hours	NLT _____
30 hours	NLT _____

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data from the first three production size batches in a supplemental application. A "Special Supplement - Changes Being Effected" (CBE-0) should be submitted when there are no revisions to be proposed to the "interim" specifications or the proposed final specifications are tighter than the "interim" specifications. In all other instances, a Prior Approval Supplement should be submitted.

Under Section 506A 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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit,

in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

Sincerely yours,

Set/for  
5/20/2004  
Gary Buehler

Director

Office of Generic Drugs

Center for Drug Evaluation and Research