



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 76-323

Food and Drug Administration  
Rockville MD 20857

AUG 10 2004

Bedford Laboratories  
Attention: Molly L. Rapp  
300 Northfield Road  
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Esmolol Hydrochloride Injection, 10 mg/mL, packaged in 100 mg/10 mL single-dose vials.

Reference is made to the Tentative Approval letter issued by this office on June 26, 2003, and to your amendments dated October 27, December 16, and December 22, 2003, and May 28 and June 1, 2004. We also acknowledge receipt of your correspondence dated April 22, May 8, and May 24, 2002 addressing the patent issues noted below.

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 Esmolol Hydrochloride Injection, 10 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Brevibloc<sup>®</sup> Injection, 10 mg/mL, of Baxter Healthcare Corporation).

The listed drug product (RLD) referenced in your application, Brevibloc<sup>®</sup> Injection, 10 mg/mL, of Baxter Healthcare Corporation, is subject to periods of patent protection. As noted in the Agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. 6,310,094 (the '094 patent) is scheduled to expire on July 12, 2021, and U.S. Patent No. 5,017,609 (the '609 patent) is scheduled to expire on November 21, 2008. Your application contains patent certifications to the '094 and '609 patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the

'094 and '609 patents will not be infringed by your manufacture, use, or sale of Esmolol Hydrochloride Injection, 10 mg/mL, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Bedford Laboratories (Bedford) for infringement of the '094 and/or the '609 patents which were the subjects of the paragraph IV certifications. This action must have been brought against Bedford prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(I) was received by the NDA/patent holders. You have notified the Agency that Bedford complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for infringement of either the '094 or 609 patents was brought against Bedford within the statutory forty-five day period. In addition, the Agency has determined that notification of U.S. Patent No. 6,528,540 (the '540 patent) by the NDA holder was received by the Agency more than 30 days after the patent was issued by the U.S. Patent and Trademark Office (PTO). Therefore, with respect to this ANDA, under 21 CFR 314.94(a)(12)(vi), Bedford is not required to submit an amended patent certification to address this patent.

We note that Baxter's formulation of Brevibloc Injection, 10 mg/mL, which you have cited as the reference listed drug product is no longer being marketed in the United States. Baxter has replaced this formulation with a new formulation containing sodium chloride as an additional inactive ingredient. The Agency has moved Baxter's original formulation for Brevibloc Injection, 10 mg/mL, to the discontinued section of the "Orange Book". However, the Agency has also made the determination that the original formulation was not withdrawn from sale for reasons of safety or effectiveness. This determination was published in the Federal Register on August 4, 2004 (69 FR 47155) and allows the Agency to review and approve ANDAs for the formulation provided by Baxter's discontinued drug product.

With respect to 180-day generic drug exclusivity, we note that Bedford Laboratories was the first ANDA applicant to submit a substantially complete ANDA with paragraph IV certifications to the '094 and '609 patents. Therefore, with this approval Bedford Laboratories is eligible for 180-days of market exclusivity for Esmolol Hydrochloride Injection, 10 mg/mL.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner.

Please submit correspondence to your application stating the date you commence commercial marketing of this product.

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

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

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-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours, 

(b)(6)

Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research