DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

NDA 50-697/S-002
NDA 50-698/S-014

Abbott Laboratories
Attention: Mr. Greg Bosco
Senior Product Manager
D-491/AP6B-1SW
100 Abbott Park Road
Abbott Park, IL 60064-6108

Dear Mr. Bosco:

Please refer to your New Drug Applications (NDAs) for Biaxin® Filmtab® and Biaxin® Granules.

We note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

A. Accelerated Approval

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
Biaxin® Filmtab® (clarithromycin tablets)	50-697	S-002	July 26, 2001	July 27, 2001
Biaxin® Granules (clarithromycin for oral suspension)	50-698	S-014	July 27, 2001	July 30, 2001

NDAs 50-697 and 50-698 were approved on December 23, 1993 under the regulations for accelerated approval of new drugs for serious or life-threatening illnesses (21 CFR 314.510) for the treatment of disseminated mycobacterial infections due to *Mycobacterium avium* and *Mycobacterium intracellulare.* In the approval letter, the following commitments were acknowledged (dates of responses to these commitments are in italics):

1. Abbott will assist the (b)(4 with the large MAC survival study, Protocol (b)(4) which will study clarithromycin 5) BID versus clarithromycin 1000 mg BID as a multiple drug regimen. Abbott will provide support over the first 12 weeks of the study so that data can be accumulated and presented regarding mortality. One goal of this study is to resolve the issue of differential mortality at the 500 mg and 1000 mg BID doses previously observed in the Abbott M90-500 study. [*A response to Commitment 1 was included in the July 26, 2001 submission to NDA 50-697/S-002 and the July 30, 2001 submission to NDA 50-698/S-014.]*

2. Abbott will conduct a two-arm study with forty patients per arm, comparing clarithromycin plus one other drug to clarithromycin plus two other drugs. The patients will be followed for microbiology and clinical signs and symptoms every four weeks for a twenty-four week period, and followed for survival beyond twenty-four weeks. The goals of this study are to determine the tolerability of multiple drug therapy, and to assess the effect of combination therapy on the emergence of resistance. [*The response to Commitment 2 was submitted on February 24, 1997 as NDA 50-662/ S-018 (Biaxin® Filmtab).*]

3. During the same timeframe as the two previous commitments, Abbott will conduct microbiologic validation studies for clarithromycin when used as an antimycobacterial, following a protocol agreed upon with the Division. [*Responses to Commitment 3 were submitted on August 26, 1997, January 28, 1998, and January 28, 1999 to (b)(4) , on July 25, 2001 to NDA 50-697/S-001, and on July 27, 2001 to NDA 50-698/S-013.*]

In supplemental new drug applications NDA 50-697/S-002 and NDA 50-698/S-014, you requested removal from accelerated approval under 21 CFR 314.510.

We have completed the review of these supplemental applications and have concluded that adequate information has been provided. Accordingly, these supplemental applications are approved effective on the date of this letter. Approval of these supplements fulfills your commitments made under 21 CFR 314.510 and 314.550.

B. Postmarketing Commitments

We have received your submission dated March 10, 1995 ((b)(4) larithromycin), reporting on the following postmarketing study commitments:

4. Please conduct a study to determine the drug interaction or lack of drug interaction between clarithromycin and the antiretrovirals, zidovudine and didanosine, in both adults and children.

5. It is strongly recommended that you perform a drug interaction study between clarithromycin and fluconazole.

We have reviewed your submission and conclude that the above commitments were fulfilled. This completes all of your postmarketing study commitments acknowledged in our December 23, 1993 letter.

C. Request for Labeling Revision

During our review of the above submissions, we reviewed the package inserts approved on December 23, 1993 (NDA 50-697) and June 5, 2000 (NDA 50-698/S-011). We request that the following change in the labeling be made to furnish adequate information for the safe and effective use of these drugs:

- The current label addresses the increased microbiological efficacy of high doses (1000 mg and 2000 mg BID) for MAC infection, both in terms of time to first negative culture and time to 1 log decrease in CFU. However, the section on "survival" indicates higher death rates with doses greater than 500 mg bid. These conflicting data on the usefulness of higher doses may be confusing to the practitioner. In view of the overriding safety concern with doses higher than 500 mg BID, we believe that the microbiological efficacy of higher doses is not helpful to the clinician and should be removed from the label.

Please submit draft labeling as prior approval supplements to these new drug applications. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submissions provide a highlighted or marked-up copy that shows the changes that are being made.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. All 15-day reports, periodic adverse drug experience reports, field alerts, annual reports, supplements, and other submissions (except those to pending supplement NDA 50-697/S-001) should be addressed to NDA 50-662 for Biaxin® Filmtab®, not to NDA 50-697. After approval of NDA 50-697/S-001, no future submissions should be made to NDA 50-697.

If you have any questions, call Diana Willard, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
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/

Renata Albrecht

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