CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-775/S-004

MEDICAL REVIEW

Medical Officer's Review of Labeling Supplement

1.0 Identification: NDA 50-775/S-004

1.1 Applicant Information: Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108
Contact Person: Greg Bosco
Sr. Product Manager
Pharmaceutical Products Division
Regulatory Affairs
Telephone No. (847) 937-6970

1.2 Submission/Review Dates

Date of submission: July 17, 2001
Date assigned to current reviewer: July 25, 2002
Date of 1st draft review completed: December 30, 2002
Date of Final review completed: April 1, 2003

1.3 Drug Identification

Generic Drug Name: Clarithromycin
Trade Name: **BIAXIN®XL** Filmtab®
Dosage Form, Strengths, and Route of Administration: 500 mg extended-release tablets for oral administration

Category: Macrolide

2.0 Purpose of Supplement

This supplement, Changes being Effected labeling supplement, is submitted to provide proposed changes to the product labeling of Biaxin XL. The revisions to the **ADVERSE REACTIONS** – *Post-Marketing Experience* and **DOSAGE AND ADMINISTRATION** sections of the package insert include updated information from postmarketing experience with Biaxin XL tablets.

3.0 Submitted materials

One volume submitted containing the following sections: Cover Letter dated July 17, 2001; Completed Form FDA 356h; Attachment I (packaged insert of Biaxin XL®Filmtab® with proposed revisions in highlighted text); and Attachment II (supporting documentation from post-marketing experience).

4.0 Applicant's Proposed Revisions in the packaged insert of Biaxin XL®Filmtab®

The following proposed selected revisions are as follows:

A. **ADVERSE REACTIONS** section:

The following proposed revisions will be added as the new fourth paragraph under the *Post-Marketing Experience* subsection which read as follows: "There have been postmarketing reports of BIAXIN XL tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times."

MO Comment: This revision is acceptable.

B. **DOSAGE AND ADMINISTRATION** section:

The following proposed revision will be added to the first paragraph under this section which reads as follows: "BIAXIN XL tablets should be swallowed whole and not chewed, broken or crushed."

MO Comment: This revision is acceptable.

5.0 Review of the Supporting Information

I. Information to support the proposed revision in the ADVERSE REACTIONS section under Post-Marketing Experience.

According to the applicant, spontaneous adverse drug event database for Biaxin XL was reviewed by examining COSTART terms organized by body system for the time period of its approval, March 03, 2000 through May 03, 2001. There have been 41 reports of "tablets in the stool" coincident with Biaxin XL therapy. The gender distribution included 13 males, 24 females and 4 reports with an unspecified gender. The ages ranged from 12 to 87 years (n=28) with a median age of 39 years. Twenty of the 41 reports described

patients with a gastrointestinal (GI) condition, which may have resulted in a shortened GI transit time. The reports described patients with an anatomic shortening of the GI tract such as an ileostomy, colostomy or bowel resection as well as reports in patients with irritable bowel syndrome, or colitis, not otherwise specified. Three of the 41 reports of "tablet in the stool" indicated that the patients had either not taken or had inconsistently taken Biaxin XL tablets with food. The current Biaxin XL package insert recommends dosing of Biaxin XL tablets with food. According to the applicant, when two of these patients subsequently took Biaxin XL with food, they observed no recurrence of "tablet in the stool". Three of 41 postmarketing reports included information regarding both the dosing circumstances and the underlying gastrointestinal status. In these three reports, Biaxin XL was dosed with food in patients without a known underlying GI condition. The data for the remaining 15 reports was unobtainable and therefore, evaluation of these reports was limited. The applicant contends that despite their requests for follow-up information, no further information regarding either the dosing circumstances and/or the underlying gastrointestinal condition of the patients was provided.

In summary, among the 26 reports providing information, 20 (77%) had a GI condition potentially resulting in a shortened GI transit time. Three of 26 (12%) patients did not consistently take Biaxin XL tablets with food. Three of 26 (12%) had neither of these complicating factors. According to the applicant, as this extended release product is absorbed throughout the entire GI tract, conditions resulting in rapid GI transit may have contributed to the observation of Biaxin XL tablets in the stool. Therefore, the applicant proposes the label change to highlight that reports of "tablet in the stool" have been seen in patients with GI conditions.

II. Information to support the proposed revision in the DOSAGE AND ADMINISTRATION section

There have been two postmarketing reports of "tablet in the stool"describing patients who broke or crushed the Biaxin XL tablets subsequent to the observation. The *in vivo* performance of the Biaxin XL is dependent on administering the tablet as a whole. Therefore, the applicant proposes that a revision in the label should be added to indicate that Biaxin XL tablets should be swallowed whole.

6.0 Conclusion and Recommendation

It is recommended that the Labeling Supplement for NDA 50-775/S-004 be approved.

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

/s/

Alma Davidson
4/3/03 01:57:17 PM
MEDICAL OFFICER

John Alexander
4/3/03 03:30:55 PM
MEDICAL OFFICER