CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-662 /S-030, S-031

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW OF NDA 50-662/SLR030, SLR031

Date Submitted: August 31, 2000
October 20, 2000
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October 23, 2000
MOR Initiated: February 28, 2002
MOR Completed: March 14, 2002

Applicant: **Abbott Laboratories**
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

APPEARS THIS WAY
ON ORIGINAL

Drug: Biaxin® Filmtab®

Dosage: 250 mg/500 mg tablet

Background:

The purpose of these supplements is to provide changes to the product labeling. Revisions are proposed to the **CONTRAINDICATIONS, ADVERSE REACTIONS** – *Post-Marketing Experience* and **PRECAUTIONS** – *Drug Interactions, Information to Patients sections* of the package insert. Also included in the submission is a proposed **OVERDOSAGE** section.

Clinical Review of the Draft Labeling:

Under the **CONTRAINDICATIONS** section, addition of astemizole is proposed. The proposed change is made because of potential medical consequences of co-administration of these two medications. Thus, astemizole is moved from the *Drug Interactions* section to the **CONTRAINDICATIONS** section.

[redacted]. The proposed changes to the **CONTRAINDICATIONS** section are as follows:

> Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. There have been postmarketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with cisapride, pimozide, astemizole, or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to the inhibition of metabolism of these drugs by erythromycin and clarithromycin. Fatalities have been reported.

Medical Officer's Comments:

The package insert for E.E.S. has the following statement – "Concomitant administration of astemizole and erythromycin is contraindicated."
Though there have been no postmarketing clarithromycin reports of drug interaction with astemizole, clarithromycin is a macrolide similar to erythromycin; thus, there is a potential of adverse drug-drug interaction.
Note that astemizole is no longer marketed in the United States, but listing in the CONTRAINDICATIONS section is still appropriate because it might be available to patients through other means.

The proposed changes are acceptable.

Under the **PRECAUTIONS** section, the following changes have been proposed:

Information to Patients:

The following statement has been added to this section:

> Biaxin may interact with some drugs; therefore patients should be advised to report to their doctor the use of any other medications.

Medical Officer's Comments:

The proposed statement is acceptable.

Drug Interactions:

The last six paragraphs in this section have been revised to reflect the current understanding of the role of CYP3A inhibition in drug metabolism.

Those interactions based on CYP3A inhibition are listed separately from those that are not. Medications with potentially significant consequences of CYP3A based drug interactions have been identified and are included in the revision of this section. Those drugs include methylprednisone, quinidine, sildenafil, cilostazol, midazolam, and alprazolam. The sponsor in support of these changes has provided the following additional information:

A. Although there have been no reports of drug interaction with concomitant methylprednisone in the Biaxin postmarketing adverse events database, methylprednisone was added to the *Drug Interactions* section based on published data.[1]
This article describes a significant decrease in methylprednisone clearance and increased mean plasma concentrations following two days of methylprednisone 40 mg/1.72m^2 (maximum dose of 40 mg daily) after a nine day course of Biaxin 500 mg twice daily in six adult asthma patients.

B. There have been six postmarketing reports of drug interaction or increased quinidine level coincident with clarithromycin use. Two of these reports described torsades de pointes occurring as a consequence of this interaction. Although these reports of torsades de pointes were medically complicated by underlying cardiac disease or concurrent cisapride therapy, quinidine has been added to the list of drugs metabolized by CYP3A.

C. Although no clarithromycin postmarketing reports of drug interactions were received with sildenafil, cilostazol, midazolam, or alprazolam, the package inserts of these products describe potential CYP3A based interactions. Although these data are generally based on erythromycin interactions, similar CYP3A interactions may be anticipated with clarithromycin therapy:

Viagra (sildenafil): A pharmacokinetic study demonstrated a 182% increase in AUC with concomitant administration of sildenafil and erythromycin.[2]

Pletal (cilostazol): A pharmacokinetic study demonstrated an increase in AUC for cilostazol of 73%, and for 4' – trans-hydroxy-cilostazol of 141% with concomitant administration of cilostazol and erythromycin.[3]

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[1] Fost DA, Leung DYM, Martin RJ, et al. Inhibition of methylprednisone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol.* 1999;103;1031-5.
[2] Viagra package insert, Pfizer, Inc. 1999.
[3] Pletal package insert, Pharmacia and Upjohn Company, 1999.

Xanax (alprazolam): Clinical studies with similar benzodiazepines or *in vitro* studies with alprazolam suggest a possible interaction with alprazolam and macrolide antibiotics such as erythromycin and clarithromycin; caution is advised during coadministration.[4]

Versed (midazolam): Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the P450 3A4 enzyme system, including erythromycin, as prolonged sedation may result.[5]

Based on the above information, the proposed revised wording for part of the *Drug Interactions* subsection is as follows:

Erythromycin and clarithromycin are substrates and inhibitors of the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A). Coadministration of erythromycin or clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin or erythromycin.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other drugs metabolized by the CYP3A isoform are also possible. Increased serum concentrations of carbamazepine and the active acid metabolite of terfenadine were observed in clinical trials with clarithromycin.

The following CYP3A based drug interactions have been observed with erythromycin products and/or clarithromycin in postmarketing experience:

Ergotamine/dihydroergotamine: Concurrent use of erythromycin or clarithromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

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[4] Xanax package insert, Pharmacia and Upjohn Company, 1999.
[5] Versed package insert, Roche Pharmaceuticals, 1999.

Triazolobenziodiazepines (such as *triazolam* and *alprazolam)* and *related benzodiazepines (*such as *midazolam)*: Erythromycin has been reported to decrease the clearance of triazolam and midazolam, and thus, may increase the pharmacologic effect of these benzodiazepines. There have been postmarketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam.

HMG-CoA Reductase Inhibitors: As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Sildenafil (Viagra): Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. A similar interaction may occur with clarithromycin; reduction of sildenafil dosage should be considered. (See Viagra package insert.)

There have been spontaneous or published reports of CYP3A based interactions of erythromycin and/or clarithromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisone, cilostazol, and bromocriptin.

Medical Officer's Comments:

In the sponsor's submitted draft labeling, disopyramide is misspelled.

Concomitant administration of clarithromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS.)**

In addition, there have been reports of interactions of erythromycin or clarithromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

As the last paragraph in this section, the following statement has been added:

There have been postmarketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Serum levels of these medications should be monitored during clarithromycin therapy.

Medical Officer's Comments:

There was some concern voiced by Dr. Bonapace about the practicality of doing serum levels of quinidine and disopyramide. Dr. Targum, a cardiologist in the division of Cardio-Renal Drugs was consulted to render her opinion. Her comments regarding the above statement were that, given the life-threatening nature of torsades, there should be a statement about monitoring EKGs and QT interval in patients receiving clarithromycin concurrently with quinidine or disopyramide.
The revision of the format of the "Drug Interactions" section to reflect the current understanding of role of CYP3A inhibition in drug metabolism is acceptable. Dr. Charles Bonapace (Division of Biopharmaceutics) was consulted to review this section, and he concurs with the sponsor's format and revised labeling of this section.

The last paragraph of this section should be moved before the statement on ergotamine and revised as follows:

Antiarrhythmics: There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should also be monitored.

Under the **ADVERSE REACTIONS** – *Post-Marketing Experience* section, the following additions have been proposed:

To the first paragraph under this section, pancreatitis has been added to the list of reported adverse events. Convulsions has been included in the list of transient CNS events in the second paragraph. In support of these inclusions, the sponsor has submitted a summary of spontaneous adverse drug event (ADE) reports for the time period 10/31/91 to 4/12/00.

There were a total of 76 postmarketing reports of patients who developed pancreatitis while on Biaxin therapy. Twenty-six of those reports had compounding factors that caused pancreatitis such as AIDS related illnesses, and alcohol abuse. Twenty-eight reports were associated with use of concomitant medications. The remaining 22 reports described no definitive alternative etiology. Thirteen of those reports did not provide amylase or lipase levels. However, there were 9 reports in which the reported amylase and lipase levels were consistent with diagnosis of pancreatitis.

There were 108 reports of convulsions in patients on clarithromycin therapy. Sixty-four of these reports had probable other etiologies for development of seizures such as seizure disorders, HIV-related illnesses, hyponatremia, or other underlying CNS disorders. Three reports were in patients using concomitant therapies. Of the remaining 41 reports with no definitive reported etiologies, most of them had incomplete data. However, seven of these 41 reports described patients with no known previous seizure history and normal neurological evaluations before Biaxin therapy.

Medical Officer's Comments:

Based on the summary of post-marketing adverse drug event reports submitted, the addition of pancreatitis and convulsions to the Post-Marketing Experience section is acceptable.

Addition of an **OVERDOSAGE** section is proposed.

The sponsor has data on 79 reports of overdose coincident with clarithromycin use. The events most frequently reported were associated with the GI system such as abdominal pain, vomiting, nausea, and diarrhea. The proposed wording for this section is as follows:

[

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Medical Officer's Comments:

The OVERDOSAGE section should be revised as follows:

> *Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.*
> *Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.*

Medical Officer's Recommendations:

Revisions proposed to the CONTRAINDICATIONS, ADVERSE REACTIONS – Post-Marketing Experience and Information to Patients sections of the package insert are all acceptable. The OVERDOSAGE section should be revised as follows:

> *Overdosage of clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.*
> *Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.*

The last paragraph in the PRECAUTIONS – Drug Interactions section should be moved before the statement on ergotamine and revised as follows (in bold):

> **Antiarrhythmics: There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should also be monitored.**

In the sponsor's submitted draft labeling, disopyramide is misspelled.

The above recommendations should be conveyed to the sponsor of this NDA.

Nasim Moledina, M.D.
Medical Officer, DAIDP

cc: **NDA 50-662/SLR-030**
NDA 50-662/SLR-031
HFD-520
HFD-520/MO/NMoledina
HFD-520/PM/JMilstein
HFD-520/MTL/JAlexander
HFD-520/Pharm/KSeethaler
HFD-520/Micro/HSilver
HFD-520/Chem/AYu
nm/3/15/2002; rev4/25/2002.

Concurrence only:
HFD-520/Div/Dir/JSoreth

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Nasim Moledina
4/29/02 08:02:23 AM
MEDICAL OFFICER
Comments sent to sponsor on 4/26/2002
Final draft signed off on 4/26/2002

John Alexander
4/29/02 08:49:57 AM
MEDICAL OFFICER

MO Review of Biaxin labeling supplements, changes to drug interactions subsection, and Overdosage section added.

Janice Soreth
4/29/02 04:05:18 PM
MEDICAL OFFICER