# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# 50-662 /S-030, S-031

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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| NDA# | 50-662 (Supplements 030 and 031) |
| DRUG NAME | Clarithromycin (Biaxin®) |
| FORMULATIONS | Clarithromycin 250 and 500 mg tablets, clarithromycin XL 500 mg tablets, clarithromycin for oral suspension |
| SUBMISSION DATES | August 31, 2000, October 20, 2000 |
| SPONSOR | Abbott Laboratories, Abbott Park, IL 60064-6108 |
| REVIEWER | Charles R. Bonapace, Pharm.D. |
| ACTING TEAM LEADER | Sue-Chih Lee, Ph.D. |

## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

**BACKGROUND:**
The sponsor provided proposed labeling changes to the product labeling. The sections of the label that are affected by the labeling supplement includes ADVERSE REACTIONS - Post-Marketing Experience, PRECAUTIONS - Information to Patients, PRECAUTIONS - Drug Interactions, OVERDOSAGE, and CONTRAINDICATIONS.

**RESULTS:**
The sections of the label that involved changes requiring the input from Clinical Pharmacology and Biopharmaceutics included PRECAUTIONS - Information to Patients, PRECAUTIONS - Drug Interactions, OVERDOSAGE, and CONTRAINDICATIONS.

PRECAUTIONS - Information to Patients
This section of the label now includes the wording "Biaxin may interact with some drugs; therefore, patients should be advised to report to their doctors the use of any other medications".

PRECAUTIONS - Drug Interactions
This section has been revised to reflect the role of cytochrome 3A4 (CYP3A4) inhibition in drug metabolism. Drug interactions that are based on CYP3A4 inhibition are distinguished from those that are not.

Additional data on specific drugs have been added to the CYP3A4 based drug interactions section. The specific drugs include the following:

1) Methylprednisolone - Based on a published drug interaction study between clarithromycin and methylprednisolone that described a decrease in methylprednisolone clearance and increased mean plasma methylprednisolone concentrations, methylprednisolone is now included under the section of spontaneous or published reports of CYP3A4 based interactions of erythromycin and/or clarithromycin.

2) Quinidine - Based on six post-marketing reports of drug interactions between clarithromycin and quinidine that demonstrated increased quinidine concentrations with clarithromycin use, quinidine is now included under the section of spontaneous or published reports of CYP3A4 based interactions of erythromycin and/or clarithromycin. Two of the six post-marketing reports described torsades de pointes occurring as a consequence of this interaction.

3) Alprazolam- The labeling of this product states that clinical studies and *in vitro* studies with benzodiazepines other than alprazolam suggest a possible interaction with alprazolam and macrolide antibiotics such as erythromycin and clarithromycin; caution is advised during co-administration. Thus, it

is now included under the section of triazolobenziodidiazepines (such as triazolam and alprazolam) and related benzodiazepines (such as midazolam). There are no post-marketing reports of a drug interaction between clarithromycin and alprazolam.

4) Midazolam - The labeling of this product advises caution when midazolam is administered concomitantly with drugs that are known to inhibit the P450 3A4 enzyme system, including erythromycin, as prolonged sedation may result. Thus, it is now included under the section of triazolobenziodidiazepines (such as triazolam and alprazolam) and related benzodiazepines (such as midazolam). There are no post-marketing reports of a drug interaction between clarithromycin and midazolam.

5) Sildenafil - The labeling of this product describes a study demonstrating a 182% increase in the AUC of sildenafil with concomitant administration of erythromycin and sildenafil; a similar interaction may occur with clarithromycin. Thus, it is now included under its own section stating that erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. There are no post-marketing reports of a drug interaction between clarithromycin and sildenafil.

6) Cilostazol - The labeling of this product describes a study demonstrating an increase in the AUC for cilostazol and 4'-trans-hydroxy-cilostazol (one fifth as active as cilostazol) of 73% and 141%, respectively, with concomitant administration of erythromycin and cilostazol. Thus, it is now included under the section of spontaneous or published reports of CYP3A4 based interactions of erythromycin and/or clarithromycin. There are no post-marketing reports of a drug interaction between clarithromycin and cilostazol.

OVERDOSAGE:
The overdose section states that there are 79 reports of overdose with clarithromycin. As with other macrolides, clarithromycin plasma levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis due to the large apparent volume of distribution (erythromycin 0.78 L/kg, clarithromycin 2.6 L/kg, and azithromycin 31 L/kg).

CONTRAINDICATIONS:
The current clarithromycin label states that concomitant administration of erythromycin and astemizole is contraindicated based on reports of an interaction between erythromycin and astemizole resulting in QT prolongation and torsades de pointes. Since clarithromycin is also metabolized by cytochrome P450, the label states concomitant administration of clarithromycin with astemizole is not recommended. Although there have been no post-marketing drug interaction reports between clarithromycin and astemizole, in consideration of the potential medical consequences of co-administration of these two drugs, astemizole should be added to the CONTRAINDICATIONS section.

**COMMENTS:**
1) Due to post-marketing reports of torsades de pointes occurring with concomitant use of clarithromycin and quinidine or disopyramide, the sponsor recommends monitoring serum levels of these medications during clarithromycin therapy. This recommendation is acceptable to the reviewer if assays to quantitate quinidine and disopyramide concentrations are commercially available.

2) The overdosage section states that the most common adverse events were gastrointestinal based on data from 79 reports of overdose with clarithromycin. The sponsor is encouraged to quantitate the degree of overdose by giving an estimate of the number of ingested tablets and the corresponding adverse events.

3) Labeling supplement 031 recommends adding a sentence to the PRECAUTIONS - information to patients and a sentence to PRECAUTIONS - drug interactions sections. The sponsor is encouraged to

clarify whether these two sentences are additions to labeling supplement 030 and whether they will replace any recommendations from supplement 030.

4) Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for macrolide antibiotics such as erythromycin and clarithromycin. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for sertraline and paroxetine, whereas data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. It is unknown whether *in vitro* studies have been performed between clarithromycin and alprazolam. Since clarithromycin and alprazolam are metabolized by CYP3A4, the potential for a drug interaction between clarithromycin and alprazolam exists and should be reported in the label.

**RECOMMENDATIONS:**
This supplement was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation III and found to be acceptable from a clinical pharmacology point of view.

Please forward comments #1-3 to the sponsor and comments #1-4 to the reviewing medical officer.

**REFERENCES:**
1. Fost DA, Leung DYM, Martin RJ, et al. Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. J Allergy Clin Immunol. 1999;103:1031-1035.

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Division of Pharmaceutical Evaluation III

RD/FT Initialed by Sue-Chih Lee, Ph.D., Acting Team Leader_____

cc:
Division File: NDA 50-662
HFD-520 (CSO/Dillon-Parker)
HFD-880 (Division File, Lazor, Lee, Bonapace)
CDR (Clin. Pharm./Biopharm.)

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4/19/02 03:31:22 PM
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