CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050824Orig1s000

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

NDA #: 50824
(SDN 18)

REVIEWER : Anne Purfield
CORRESPONDENCE DATE: 12-07-10
CDER RECEIPT DATE : 12-08-10
REVIEW ASSIGN DATE : 12-14-10
REVIEW COMPLETE DATE: 1-10-11

SPONSOR: DAVA Pharmaceuticals, Inc.
Parker Plaza
400 Kelby Street, 10th Floor
Fort Lee, New Jersey 07024

DRUG CATEGORY: Antibacterial

INDICATION: Treatment of *Helicobacter pylori* infection and duodenal ulcer disease in adults

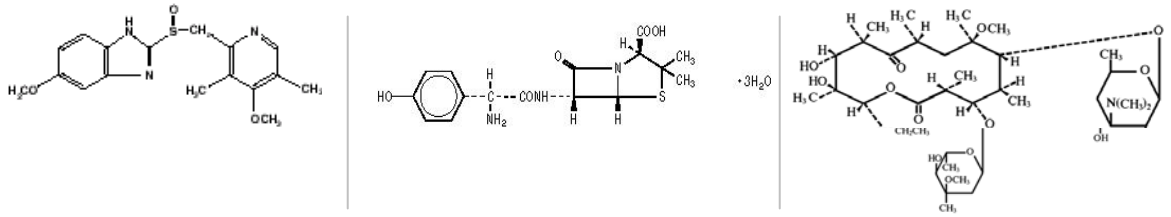
DOSAGE FORM: Blister Pack containing:
1. Omeprazole Delayed-release Capsules, 20 mg (x 2)
2. Clarithromycin Tablets, 500 mg (x 2)
3. Amoxicillin Capsules, 500 mg (x 4)

PRODUCT NAMES:

a. PROPRIETARY: To be determined

b. NONPROPRIETARY: Omeprazole, Clarithromycin and Amoxicillin

c. CHEMICAL: Omeprazole: 5-methoxy2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]1*H*-benzimidazole
Clarithromycin: 6-*O*-methylerythromycin
Amoxicillin: (2S, 5R, 6R)-6-[(R)-(-)-2-amino-2-(p-hydroxyphenyl)acetamido] 3,3-dimethyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0] heptane-2-carboxylic acid trihydrate



STRUCTURAL FORMULA:

	Omeprazole	Amoxicillin	Clarithromycin
Molecular weight:	345.42	419.45	747.96
Molecular formula:	$C_{17}H_{19}N_3O_3S$	$C_{16}H_{19}N_3O_3S\,H_2O$	$C_{38}H_{69}NO_{13}$

SUPPORTING DOCUMENTS:

1. Introduction and Background

The applicant submitted a 505(b)(2) application for the combination pack consisting of omeprazole delayed-release capsules (Prilosec®; 20 mg), clarithromycin (Biaxin®; 500 mg) and amoxicillin (Amoxil®; 500 mg) for the treatment of *Helicobacter pylori* infection and duodenal ulcer disease in 2009. The Division issued a complete response letter dated 7/20/10, which included proposed changes to the microbiology section of the labeling (see microbiology review dated 6/30/10). The sponsor has submitted a response to the Division's complete response letter (resubmission, Class 1) with proposed labeling.

2. The Labeling

2.1. Sponsor's version of the labeling

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Omeprazole is an antisecretory drug (b) (4) .

12.4 Microbiology

Mechanism of Action:

Omeprazole, an antisecretory drug with the substituted benzimidazoles, suppresses gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-dependent and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Omeprazole can also exhibit anti-bacterial activity depending on the culture conditions. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Clarithromycin exerts its antibacterial activity by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis.

Amoxicillin acts through the inhibition of biosynthesis of cell wall mucopeptide.

Activity *in vitro* and *in vivo*:

Triple therapy with omeprazole, clarithromycin and amoxicillin has been shown to be active against most strains of *Helicobacter pylori in vitro* and in clinical infections as indicated [*See Indications and Usage (1.1)*].

In vitro studies show that chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with bactericidal effects of penicillin; however, the clinical significance of this interaction is not well documented.

Drug Resistance:

Helicobacter pylori Pretreatment Resistance

Clarithromycin pretreatment resistance rates were 9.3% (41/439) in omeprazole / clarithromycin / amoxicillin triple therapy studies [*See Clinical Studies (14.1)*].

Amoxicillin pretreatment susceptible isolates (≤ 0.25 µg/mL) were found in 99.3% (436/439) of the patients in the omeprazole / clarithromycin / amoxicillin triple therapy studies (1, 2, and 3). Amoxicillin pretreatment minimum inhibitory concentrations (MICs) > 0.25 µg/mL occurred in 0.7% (3/439) of the patients, all of whom were in the clarithromycin and amoxicillin study arm. One patient had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) of > 256 µg/mL by Etest®.

Table 2 Pre-treatment and post-treatment clarithromycin susceptibility test results and clinical / bacteriological outcomes in patients treated with triple therapy*

Clarithromycin Pre-treatment Results		Clarithromycin Post-treatment Results			
	H. pylori negative – eradicated	*H. pylori* positive – not eradicated Post-treatment susceptibility results			
		S [a]	I [a]	R [a]	No MIC
Susceptible [a] 171	153	7	0	3	8
Intermediate [a] 0	0	0	0	0	0
Resistant [a] 14	4	1	0	6	3

[a] Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 µg/mL, Resistant (R) MIC ≥ 1 µg/mL
* Treatment with omeprazole 20 mg twice daily / clarithromycin 500 mg twice daily / amoxicillin 1 g twice daily for 10 days (Studies 1,2 and 3) followed by omeprazole 20 mg once daily for another 18 days (Studies 1 and 2)

Patients not eradicated of *H. pylori* following omeprazole / clarithromycin / amoxicillin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, if possible. Patients with clarithromycin-resistant *H. pylori* should not be treated with any of the following: omeprazole / clarithromycin dual therapy, omeprazole / clarithromycin / amoxicillin triple therapy, or other regimens which include clarithromycin as the sole antimicrobial agent.

Amoxicillin Susceptibility Test Results and Clinical / Bacteriological Outcomes

In the triple therapy clinical trials, 84.9% (157/185) of the patients in the omeprazole / clarithromycin / amoxicillin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori* and 15.1% (28/185) failed therapy. Of the 28 patients who failed triple therapy, 11 had no post-treatment susceptibility test results and 17 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Eleven of the patients who failed triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs.

Susceptibility Test for *Helicobacter pylori*:

The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs [*See References (15)*]. One to three microliters of an inoculum equivalent to a No. 2 McFarland standard ($1 \times 10^7 - 1 \times 10^8$ CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥ 2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for campylobacters. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Table 3 *In vitro* Susceptibility Interpretive Criteria for Clarithromycin and Amoxicillin

Clarithromycin MIC (µg/mL) [a]	Interpretation
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1.0	Resistant (R)
Amoxicillin MIC (µg/mL) [a,b]	**Interpretation**
≤ 0.25	Susceptible (S)

[a] These are breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.
[b] There were not enough organisms with MICs > 0.25 µg/mL to determine a resistance breakpoint.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Table 4 Quality Control for Susceptibility Testing

Microorganism [a]	Antimicrobial Agent	MIC (µg/mL)
H. pylori ATCC 43504	Clarithromycin	0.015 – 0.012
H. pylori ATCC 43504	Amoxicillin	0.015 – 0.012

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Effects on Gastrointestinal Microbial Ecology:

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

15 REFERENCES

1. Clinical Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard- Eighth Edition.* CLSI document M07-A8. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.

2.2. Comments

The applicant has accepted all the changes proposed by the Division (for details see microbiology review dated 6/30/10) in sections 12.1, 12.4 and 15. The applicant has made few formatting changes that are appropriate.

3. Recommendations

This application should be approved with respect to Microbiology.

Anne Purfield
Anne Purfield, PhD
Microbiologist, DSPTP

CONCURRENCES:

DSPTP /Microbiology Team Leader *Shukal Bala* Signature 1/10/11 Date

CC:
DSPTP/Original NDA
DSPTP/PM/Judit Milstein

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/s/

ANNE E PURFIELD
01/10/2011

SHUKAL BALA
01/10/2011

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

NDA #: 50824
(SDN #3)

REVIEWER : Anne Purfield
CORRESPONDENCE DATE: 09-21-09
CDER RECEIPT DATE : 9-22-09
REVIEW ASSIGN DATE : 10-13-09
REVIEW COMPLETE DATE: 11-03-09

SPONSOR: DAVA Pharmaceuticals, Inc.
Parker Plaza
400 Kelby Street, 10th Floor
Fort Lee, New Jersey 07024

DRUG CATEGORY: Antibacterial

INDICATION: Treatment of *Helicobacter pylori* infection and duodenal ulcer disease in adults

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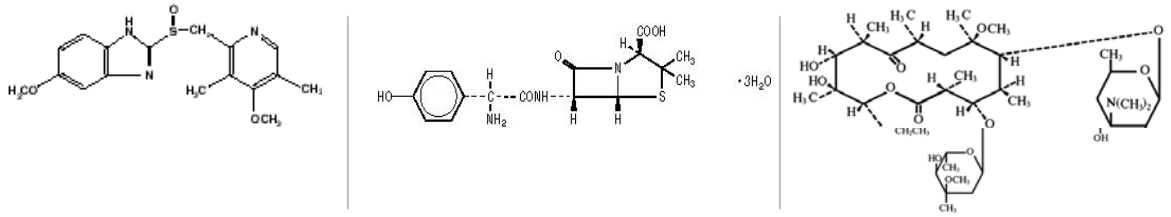

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SUPPORTING DOCUMENTS: None

Table of Contents

1. Executive Summary

The applicant has submitted a 505(b)(2) application for the combination pack consisting of omeprazole delayed-release capsules (Prilosec®; 20 mg), clarithromycin (Biaxin®; 500 mg) and amoxicillin (Amoxil®; 500 mg) for the treatment of *Helicobacter pylori* infection and duodenal ulcer disease. Several changes to the Microbiology Sections (12.1 and 12.4) of the proposed product insert are recommended, including addition of the mechanisms of action for amoxicillin and clarithromycin and updated reference for susceptibility testing method.

2. Introduction and Background

In this submission, the applicant seeks approval under 505(b)(2) for drug combination packs containing omeprazole (20 mg), amoxicillin (1000 mg), and clarithromycin (500 mg) triple combination therapy to treat patients with *Helicobacter pylori* infection and duodenal ulcer disease. Amoxicillin and clarithromycin are approved for the to treatment of *H. pylori* infection in patients with duodenal ulcer disease; the use of the three-drug combination is also approved for the treatment of *H. pylori* in patients with duodenal ulcer disease and described in the omeprazole package insert; however there is no product available that includes a combination of all three drugs.

Omeprazole is a proton pump inhibitor approved to treat duodenal ulcers, gastric ulcers, pathological hypersecretory conditions in adults, and gastroesophageal reflux disease (GERD) and erosive esophagitis in pediatric patients and adults. Amoxicillin is a semisynthetic analog of ampicillin that is approved to treat infections due to susceptible β-lactamase-negative strains of bacteria, including *H. pylori*. Clarithromycin is a broad spectrum, semi-synthetic macrolide antibiotic approved to treat mild to moderate bacterial infections caused by susceptible strains, including *H. pylori*.

There are no new studies included in the submission; the applicant's proposed package insert is based on the three Reference Listed Drugs, Prilosec® (omeprazole), Biaxin® (clarithromycin), and Amoxil® (amoxicillin).

3. The Labeling

3.1. Sponsor's version of the labeling

(b) (4)

[redacted]

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50824	ORIG-1	DAVA PHARMACEUTICALS INC	OMEPRAZOLE 25MG/AMOXOCILLIN 500MG/CLARITHROMYCIN 500MG

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/s/

ANNE E PURFIELD
06/30/2010

SHUKAL BALA
06/30/2010

MICROBIOLOGY FILING CHECKLIST

ANDA Number: 50-824 **Applicant:** DAVA Pharmaceuticals, Inc. **Filing Date:** 08/18/2009

Product Name: Omeprazole/ Clarithromycin/Amoxicillin **NDA Type:** ANDA/505(b)(2)

On **initial** overview of the ANDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the microbiology information (preclinical/nonclinical and clinical) described in different sections of the ANDA organized in a manner to allow substantive review to begin?			Not applicable
2	Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?		X	Annotated label is needed
3	Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			Not applicable
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			Not applicable
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			Not applicable
7	Has the applicant submitted the clinical microbiology datasets in a format which intents to correlate baseline pathogen with clinical and microbiologic outcome?			Not applicable
8	Has the applicant submitted draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/ANDA studies, and in a manner to allow substantive review to begin?			Not applicable
9	Has the applicant submitted a clinical microbiology dataset in an appropriate/standardized format which intents to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?			Not applicable

	Content Parameter	Yes	No	Comments
10	Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?			Not applicable
11	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
12	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?		X	
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?			Not applicable
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the ANDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The sponsor should be requested to provide the following information:

1. Please provide an annotated version of the label.
2. Please provide product insert/labels for Omeprazole Delayed-Release Capsules (ANDA #75-576), Clarithromycin Tablets (ANDA #65-178), and Amoxicillin Capsules (ANDA #62-881) for review.

_____

Anne Purfield, Ph.D. Date
Microbiology Reviewer, DSPTP

_____

Shukal Bala, Ph.D. Date
Microbiology Team Leader, DSPTP

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/s/

Anne Purfield
7/22/2009 01:37:48 PM
MICROBIOLOGIST

Shukal Bala
7/23/2009 07:51:24 AM
MICROBIOLOGIST