CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050824Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL MEMORANDUM

NDA	50-824
Submission date	02/07/2011
Contains	Labeling information
DRUG	Omeprazole 20-mg delayed-release capsules USP, Amoxicillin 500-mg capsules USP, and Clarithromycin 500-mg tablets USP
SPONSOR	DAVA Pharmaceuticals, Inc.
INDICATION	Treatment of *H. Pylori* infection and duodenal ulcer disease in adults
STATISTICAL REVIEWER	Lan Zeng
MEDICAL REVIEWER	Joette Meyer
PROJECT MANAGER	Judit Milstein

The current submission dated February 7, 2011 contains a revised labeling on a co-packaged product of OMEPRAZOLE DELAYED-RELEASE CAPSULES, CLARITHROMYCIN TABLETS, and AMOXICILLIN CAPSULES from DAVA Pharmaceuticals, Inc. This reviewer evaluated the proposed Section 14 Clinical Studies and determined that it is acceptable from statistical point of view. A complete statistical review of the original NDA can be found in DARRTS.

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/s/

LAN ZENG
02/07/2011

TSAE YUN D LIN
02/07/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	50-824
Drug Name:	(b) (4) (Omeprazole 20-mg delayed-release capsules, USP, Amoxicillin 500-mg capsules, USP, and Clarithromycin 500-mg tablets, USP)
Indication(s):	Treatment of *H. Pylori* infection and duodenal ulcer disease in adults
Applicant:	DAVA Pharmaceuticals, Inc.
Date(s):	Submission date: September 21, 2009 PDUFA due date: July 22, 2010
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Lan Zeng, M.S.
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Medical Division:	Division of Special Pathogen and Transplant Products
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Keywords:	NDA review, *H. Pylori*

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This application is of NDA 50-824 (originally assigned as (b) (4)) about a Patient Compliance Pack, Triple Therapy Brand Name (TTBN), for the treatment of adult patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history). The original NDA was submitted by DAVA Pharmaceuticals, Inc. (DAVA) to the Division of Special Pathogen and Transplant Products (DSPTP) on 18 June 2009. Following a teleconference on 14 August 2009 with the Division and in accordance with 505(b)(4)(A), DAVA withdrew NDA 50-824 on 20 August 2009 and resubmitted it on 21 September 2009. The NDA contains an annotated side-by-side comparison for labeling of three Reference Listed Drugs (Omeprazole, Amoxicillin, and Clarithromycin), upon which the sponsor relies for proof of safety and efficacy.
In response to the Division's information request dated 17 November 2009, the sponsor submitted a list of literature reference to address how each component of the co-packaged product contributes to the effect of the co-packaged product on 6 January 2010.

The efficacy of the proposed omeprazole plus amoxicillin plus clarithromycin triple-therapy (OAC) was examined by way of a review of published clinical data, focusing on a comparison of the triple-therapy co-packaged product to each pair of drugs (i.e., OAC vs. amoxicillin plus clarithromycin (AC), OAC vs. omeprazole plus clarithromycin (OC), OAC vs. omeprazole plus amoxicillin (OA)) in *Helicobacter pylori (H. pylori)* eradication. A total of six randomized, comparative clinical trials were identified, out of which four studies evaluated OAC versus AC, one compared OAC to OC, and the other one compared OAC to OA. In addition, a meta-analysis of 74 studies examined dual-therapy regimens with OC or OA versus triple-therapy regimen with OAC. The triple-therapy regimen consisting of omeprazole, clarithromycin and amoxicillin was more effective in eradicating *H. pylori* than dual-therapy with either amoxicillin plus clarithromycin, or omeprazole plus clarithromycin, or omeprazole plus amoxicillin. These studies are limited by the fact that only 3 studies with triple-therapy regimens were conducted in the US and had the same oral regimen as the current application.

1.2 Brief Overview of Clinical Studies

The NDA is for a Patient Compliance Pack, Triple Therapy Brand Name (TTBN), for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history) to eradicate *H. pylori* in adults. TTBN is a combination product and consists of 3 Reference Listed Drugs (RLDs) as follows: Omeprazole Delayed-Release Capsules USP 20 mg, Amoxicillin Capsules USP 500 mg, and Clarithromycin Tablets USP 500 mg. Each of these 3 active ingredients has been previously approved individually, upon which the sponsor relies for proof of safety and efficacy. According to Section 505(b)(2) of the Federal Food, Drug, and

Cosmetic Act, certain drug approvals can rely on literature or on an Agency finding of safety and/or effectiveness for an approved drug product.

No clinical data are included; instead, the submission contains an annotated side-by-side comparison for labeling content of the 3 RLDs. In response to the Division's INFORMATION REQUEST dated 17 November 2009, the sponsor submitted a list of literature reference to address the effect of individual component to the overall efficacy of the co-packaged product on 6 January 2010. These articles form the basis of this review. The efficacy of TTBN is examined by a comparison of the triple-therapy co-packaged product to each pair of drugs (i.e., OAC vs. amoxicillin plus clarithromycin (AC), OAC vs. omeprazole plus clarithromycin (OC), OAC vs. omeprazole plus amoxicillin (OA)).

1.3 Statistical Issues and Findings

A total of six randomized, comparative clinical trials were identified, out of which four (Studies 1, 2, 3, and 4) evaluated OAC versus AC, one (Study 5) compared OAC to OC, and one (Study 6) compared OAC to OA. After 10 days of treatment in Studies 1, 2, and 3, the *H. pylori* eradication rates ranged from 69% to 83% for OAC triple-therapy vs. 32% to 37% for AC dual-therapy ($p<0.001$). In Study 4, *H. pylori* eradication rate was 94% for OAC triple-therapy and 26% for AC dual-therapy ($p<0.001$) after 7 days of treatment. *H. pylori* eradication rate was 81.1% with OAC triple-therapy compared to 62.0% with OC dual-therapy ($p<0.001$) in Study 5 and 93% with OAC triple-therapy compared to 26% with OA dual-therapy ($p<0.001$) in Study 6. Additionally, a meta-analysis of 74 studies reported dual-therapy regimens consisting of OC and OA eradicated *H. pylori* infections 76% and 65% of the time, respectively, whereas, triple-therapy OAC regimens eradicated H. *pylori* 82% of the time (OAC vs. OA: $p<0.001$; OAC vs. OC: $p<0.001$). Furthermore, three US double-blind, controlled trials demonstrated that dual therapy with OA is well tolerated but the *H. pylori* eradication rate which can be expected in the US is at best 50%. The triple-therapy regimen consisting of omeprazole, clarithromycin and amoxicillin was more efficacious in eradicating *H. pylori* than dual-therapy with either amoxicillin plus clarithromycin, or omeprazole plus clarithromycin, or omeprazole plus amoxicillin. Amoxicillin appears to be the weakest component of the triple-therapy regimen as demonstrated by large contributions of omeprazole and clarithromycin and a more modest contribution of amoxicillin.

These studies are limited by the fact that only 3 studies (Studies 1, 2, and 3) were conducted in the US. Furthermore, only these 3 US studies had the same oral regimen as the current application, "Omeprazole Delayed-Release Capsules 20 mg plus Amoxicillin 1000 mg plus Clarithromycin 500 mg each given twice daily for 10 days", which is also the recommended adult dose regimen in the current omeprazole and clarithromycin labels.

2. INTRODUCTION

Please note much of the following description about H. pylori and study designs are taken from reference articles listed at the end of this review.

2.1 Overview

Helicobacter pylori (H. pylori) is one of the most common worldwide human infections and is associated with a number of important upper gastrointestinal (GI) conditions including chronic gastritis, peptic ulcer disease, and gastric malignancy. The prevalence of *H. pylori* is closely tied to socioeconomic conditions and is more common in developing countries than in developed countries. It is estimated that 30-40% of the U.S. population is infected with *H. pylori.* Although the majority of those infected remain clinically silent, there are certain clinical conditions that have been linked with *H. pylori* infection. The established indications for *H. pylori* cure include peptic ulcer, gastric mucosa associated lymphoid tissue, and uninvestigated dyspepsia. Duodenal ulcer is one kind of peptic ulcer diseases which clearly has clinical and economic merits with *H. pylori* eradication. In the United States, the primary therapies for *H. pylori* infection include: a proton pump inhibitor (PPI), clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a PPI or H_2RA, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10 to 14 days.

The current application of NDA 50-824 (originally assigned as (b) (4)) is pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act which permits reliance of certain drug approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product. The original NDA was submitted by DAVA Pharmaceuticals, Inc. (DAVA) to the Division of Special Pathogen and Transplant Products (DSPTP) on 18 June 2009. Following a teleconference on 14 August 2009 with FDA and in accordance with 505(b)(4)(A), DAVA withdrew NDA 50-824 on 20 August 2009 and resubmitted it on 21 September 2009. DAVA is seeking marketing approval for a Patient Compliance Pack, Triple Therapy Brand Name (TTBN), for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history) to eradicate *H. pylori* in adults. TTBN is a combination product and consists of 3 Reference Listed Drugs (RLDs) as follows: Omeprazole Delayed-Release Capsules USP 20 mg (ANDA 75-576, Dr. Reddy's Laboratories, Inc.), Amoxicillin Capsules USP 500 mg (ANDA 62-881, DAVA Pharmaceuticals, Inc.), and Clarithromycin Tablets USP 500 mg (ANDA 65-178, Roxane Laboratories, Inc.). Omeprazole is a proton pump inhibitor indicated for treatment of duodenal ulcer, gastric ulcer and pathological hypersecretory conditions in adults, treatment of gastroesophageal reflux disease in pediatric patients and adults, as well as maintenance of healing or erosive esophagitis in pediatric patients and adults. Amoxicillin is indicated in the treatment of infections due to susceptible (only β-lactamase-negative) strains of the designated microorganisms. Clarithromycin is indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms. All of these 3 active ingredients have been previously approved individually and have been labeled for use in *H.*

pylori eradication to reduce the risk of duodenal ulcer recurrence. The prescribing information of omeprazole has the OAC regimen which is 20 mg omeprazole plus 1000 mg amoxicillin plus 500 mg clarithromycin, all given twice daily for 10 days. In patients with an ulcer present at therapy initiation, an additional 18 days of 20 mg omeprazole once daily is recommended for ulcer healing and symptom relief. Amoxicillin 1000 mg and clarithromycin 500 mg, in combination with lansoprazole 30 mg, have also been labeled as triple therapy given twice daily for 10 or 14 days. While the OAC regimen has been labeled for the treatment of *H. pylori* infection and duodenal ulcer disease (active or 1-year history of a duodenal ulcer) as discussed above, it is the first time these drugs will be co-packaged together. Therefore, it is essential to assess the efficacy of each part of the combination.

No clinical data are included; instead, DAVA's current application for proof of safety and efficacy is based on reference to labeling for the 3 RLDs (omeprazole, amoxicillin, and clarithromycin). The Division sent to the sponsor the following INFORMATION REQUEST on 17 November 2009:

> *Please address how each component of the co-packaged product contributes to the effect of the co-packaged product. We would expect that this be done by a comparison of the co-packaged products to each pair of drugs (i.e., co-packaged product vs. amoxicillin plus clarithromycin, co-packaged product vs. amoxicillin plus omeprazole, and co-packaged product vs. omeprazole plus clarithromycin). In each comparison the co-packaged product should be superior to the pair of drugs. This information can be supported by literature references.*

DAVA submitted its response on 6 January 2010, which compared the co-packaged product to each pair of drugs using relevant published clinical data. This review will evaluate the efficacy of the proposed triple-therapy for the eradication of *H. pylori*, focusing on how each of the three components contributes to the overall efficacy of the co-packaged product.

The sponsor's proposed indication is "for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or up to 1-year history) to eradicate *H. pylori* in adults". The proposed adult oral regimen is "Omeprazole Delayed-Release Capsules 20 mg plus Amoxicillin 1000 mg plus Clarithromycin 500 mg each given twice daily for 10 days".

2.2 Data Sources

No clinical data sets were submitted. Instead, a list of literature reference were identified as most pertinent by the sponsor including five (5) clinical research articles, two (2) gastroenterology guidelines and one (1) review article.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Efficacy of Omeprazole in the Co-packaged Product (OAC versus AC)

The efficacy of omeprazole in the triple therapy (OAC) was demonstrated in 4 randomized, double-blind clinical studies in patients with *H. pylori* infection and duodenal ulcer disease (Laine et al., Studies 1, 2, 3; Lind et al., Study 4). Studies 1 and 2 were conducted in patients with an active duodenal ulcer. Study 3 was conducted in patients with a history of a duodenal ulcer in the past 5 years but without an ulcer present at the time of enrollment. Study 4 was conducted in patients with a history of at least one endoscopically documented duodenal ulcer either by the investigator or from previous endoscopies at any time in the past and a positive *H. pylori* test result (usually rapid urease test). Studies 1, 2, and 3 were conducted in the U.S. whereas Study 4 was conducted in 47 centers in France, Germany, Ireland, Norway, Sweden, and the United Kingdom.

The dose regimen in Studies 1, 2, and 3 was 10-day courses of either omeprazole 20 mg twice daily plus amoxicillin 1000 mg twice daily plus clarithromycin 500 mg twice daily (OAC); or placebo plus amoxicillin 1000 mg twice daily plus clarithromycin 500 mg twice daily (AC). Patients were randomly assigned in a 1:1 ratio to receive either OAC or AC. In Studies 1 and 2 which enrolled patients with active ulcers, patients in the OAC group received an additional 18 days of omeprazole 20 mg q.d. while those in the AC group received an additional 18 days of placebo for omeprazole. The same OAC and AC dose regimens were used in Study 4 but for a 7-day course. Study 4 had two additional dose groups: OMC (omeprazole plus metronidazole plus clarithromycin) and MC (metronidazole plus clarithromycin), which were not included in the current evaluation due to its irrelevance. A total of 539 patients were randomized resulting in 133 patients in the OAC group and 137 patients in the AC group in Study 4.

Comment: Note that the duration of triple-therapy (OAC) in Study 4 was different from the proposed oral regimen of the current application, which is "Omeprazole Delayed-Release Capsules 20 mg plus Amoxicillin 1000 mg plus Clarithromycin 500 mg each given twice daily for 10 days".

Endoscopy was performed at baseline and 4 weeks after completion of study medication (at Week 8) in Studies 1 and 2; it was performed at baseline and 4-6 weeks after the completion of therapy in Study 3 (during the period from day 38-52 of the study). Eradication of *H. pylori* was defined as no positive endoscopic biopsy test (CLOtest® histology, culture) and at least two types of tests (CLOtest®, histology, culture) were negative at final endoscopy. In Study 4, patients underwent a ^{13}C-urea breath test and endoscopy at baseline, and 4 and 8 weeks after the treatment end. Eradication was defined as a conversion from a positive *H. pylori* test by ^{13}C-urea breath and/or culture at entry to 2 negative tests 4 and 8 weeks after cessation of therapy.

Analysis of efficacy parameters was performed using both an intent-to-treat (ITT) and per-protocol (PP) population. Patients were included in the ITT analysis of Studies 1, 2, and 3 if they had documented *H. pylori* infection at baseline, had confirmed duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included in the ITT analysis as failures of therapy.

Patients were included in the PP analysis of Studies 1, 2, and 3 if they had confirmed duodenal ulcer disease and *H. pylori* infection at baseline and completed the study. If patients dropped out of the study due to an adverse event related to the study drug, they were included in the PP analysis as failures of therapy. In Study 4, patients were included in the ITT analysis if they were verified as *H. pylori* positive and took at least one study drug. Patients were excluded from the PP analysis if they were not in ITT, had unknown post treatment *H. pylori* status, poor compliance, *H. pylori* assessments performed less than 28 days after the end of therapy, or protocol deviations.

Table 1 summarizes the *H. pylori* eradication rates for each study. After 10 days of treatment in Studies 1, 2, and 3, the ITT eradication rates ranged from 69% to 83% for OAC triple-therapy vs. 32% to 37% for AC dual-therapy ($p<0.001$). Results are similar as in the omeprazole prescribing information. In Study 4, *H. pylori* eradication rates were 94% for triple-therapy and 26% for dual-therapy ($p<0.001$) after 7 days of treatment. Triple-therapy with omeprazole, amoxiciIlin and clarithromycin produced significantly higher eradication rates than did dual-therapy with amoxicillin and clarithromycin which shows the added benefit of omeprazole.

Table 1. *H. pylori* Eradication Rates in Studies 1, 2, 3, and 4

	Intent-to-Treat		**Per-Protocol**	
	OAC	AC	OAC	AC
Study 1				
Number	80	84	63	65
Eradication rate	69%	37%	78%	45%
Difference [95% CI]*	32% [16.6%, 45.8%]	-	33% [16.3%, 48.4%]	-
P-value	<0.001	-	<0.001	-
Study 2				
Number	77	83	61	66
Eradication rate	73%	36%	84%	42%
Difference [95% CI]*	37% [21.4%, 50.1%]	-	42% [24.7%, 55.8%]	-
P-value	<0.001	-	<0.001	-
Study 3				
Number	84	99	69	93
Eradication rate	83%	32%	90%	33%
Difference [95% CI]*	51% [37.8%, 62.4%]	-	57% [43.2%, 67.4%]	-
P-value	<0.001	-	<0.001	-
Study 4				
Number	127	131	110	110
Eradication rate	94%	26%	95%	25%
Difference [95% CI]*	68% [58.2%, 75.7%]	-	70% [58.7%, 77.5%]	-
P-value	<0.001	-	<0.001	-

OAC = Omeprazole 20 mg b.i.d. + Amoxicillin 1000 mg b.i.d. + Clarithromycin 500 mg b.i.d.
AC = Amoxicillin 1000 mg b.i.d. + Clarithromycin 500 mg b.i.d.
*Exact confidence intervals for the difference (OAC - AC) are computed by the reviewer. The number of eradicated cases is imputed using total number of subjects and eradication rate reported in the reference articles.

3.1.2 Efficacy of Amoxicillin in the Co-packaged Product (OAC versus OC)

The efficacy of amoxicillin in the triple therapy (OAC) was evaluated by Habu et al. in 234 patients with active gastric ulcer or duodenal ulcer in Japan (Habu et al., Study 5). Patients suffering from *H. pylori* infection proven either histologically or culturally were randomized to receive either omeprazole 20 mg b.i.d. plus amoxicillin 500 mg q.i.d. plus clarithromycin 400 mg b.i.d. (OAC); or omeprazole 20 mg b.i.d. plus clarithromycin 400 mg b.i.d. (OC) for 14 days. Subsequently, both groups were treated with omeprazole 20 mg daily for 2 weeks and with ranitidine 300 mg daily for another 4 weeks. After completion of 4-week ranitidine period, endoscopy was performed to assess ulcer healing and the status of *H. pylori* infection. *H. pylori* infection was examined histologically (hematoxylin and eosin and a Giemsa stain) and by culture. The cure of *H. pylori* infection was assumed if all tests were negative.

Comment: The triple therapy (OAC) dose regimen in Study 5 was different from the proposed oral regimen of the current application, which is "Omeprazole Delayed-Release Capsules 20 mg plus Amoxicillin 1000 mg plus Clarithromycin 500 mg each given twice daily for 10 days". In addition, omeprazole 20 mg daily was given alone for 2 weeks followed by ranitidine 300 mg daily for another 4 weeks. This information, along with those presented in Section 3.1.4, can be considered supportive evidence of the efficacy of amoxicillin.

Table 2 shows the cure rates of *H. pylori* infection in patients with duodenal ulcers were 81.1% for triple-therapy with OAC and 62.0% for dual-therapy with OC (Intent-to-treat patients). Corresponding rates in the per-protocol patients were 91.5% and 70.5%, respectively. Overall, the cure rates with triple-therapy were significantly higher than those with dual-therapy ($p<0.001$). Triple-therapy with omeprazole, amoxicillin, and clarithromycin was more effective in eradicating *H. pylori* than dual-therapy with omeprazole and clarithromycin which shows the added benefit of amoxicillin.

Comment: The reference article provided no definition for Intent-to-Treat (ITT) or Per-Protocol (PP) population. It is unclear how patients were included or excluded in the ITT or PP analysis.

Table 2. *H. pylori* Eradication Rates in Study 5

	Intent-to-Treat		**Per-Protocol**	
	OAC	OC	OAC	OC
Number	53	50	47	44
Eradication rate	81.1%	62.0%	91.5%	70.5%
Difference [95% CI]*	19% [1.4%, 6.3%]	-	21% [4.8%, 7.6%]	-
P-value	<0.05	-	<0.001	-

OAC = Omeprazole 20 mg b.i.d. + Amoxicillin 500 mg q.i.d. + Clarithromycin 400 mg b.i.d.
OC = Omeprazole 20 mg b.i.d. + Clarithromycin 400 mg b.i.d.
* Exact confidence intervals for the difference (OAC - OC) are calculated by the reviewer.

3.1.3 Efficacy of Clarithromycin in the Co-packaged Product (OAC versus OA)

The efficacy of clarithromycin in the triple therapy was studied in patients with symptoms of dyspepsia, normal gastrointestinal endoscopy examination and positive urease test on antral biopsy specimen in France (Delchier et al., Study 6). A total of 120 symptomatic patients were randomized to receive either omeprazole 40 mg b.d. plus amoxicillin 750 mg b.d. plus clarithromycin 250 mg b.d. (OAC); or omeprazole 40 mg b.d. plus amoxicillin 750 mg b.d. (OA) for 14 days. Patients underwent a ^{13}C-urea breath test for *H. pylori* assessment at baseline, on the last day of treatment, and 4 weeks after the end of treatment. Eradication of *H. pylori* was defined as a negative breath test 4 weeks after the end of treatment.

Comment: Note the triple therapy (OAC) regimen in Study 6 was different from the proposed oral regimen of the current application, which is "Omeprazole Delayed-Release Capsules 20 mg plus Amoxicillin 1000 mg plus Clarithromycin 500 mg each given twice daily for 10 days".

For efficacy analysis, an All Patient Treated population was defined excluding patients who were not treated with the combination therapy plus patients in whom assessment of *H. pylori* status was not performed at the 2-week or the 6-week visits for evaluation of clearance and eradication. A Per Protocol analysis was also utilized excluding patients with major protocol deviations.

H. pylori status is summarized in Table 3. At 4 weeks after the end of treatment, *H. pylori* was eradicated in 93% of patients receiving OAC compared to 26% of the patients receiving OA ($p<0.001$). The Per protocol analysis showed similar results. Triple-therapy with omeprazole, amoxicillin, and clarithromycin was more effective in eradicating *H. pylori* than dual-therapy with omeprazole and amoxicillin which shows the added benefit of clarithromycin.

Table 3. *H. pylori* Eradication Rates in Study 6

	All Patients Treated		**Per-Protocol**	
	OAC	OA	OAC	OA
Number	55	57	48	47
Eradication rate	93%	26%	92%	23%
Difference [95% CI]*	67% [51.1%, 78.3%]	-	69% [50.9%, 80.4%]	-
P-value	<0.001	-	<0.001	-

OAC = Omeprazole 40 mg b.d. + Amoxicillin 750 mg b.d. + Clarithromycin 250 mg b.d.
OA = Omeprazole 40 mg b.d. + Amoxicillin 750 mg b.d.
* Exact confidence intervals for the difference (OAC - OA) are calculated by the reviewer.

3.1.4 Meta-analysis (OAC versus OC or OAC versus OA)

The contribution of amoxicillin or clarithromycin to the co-packaged product was further supported by a meta-regression analysis of published studies through April 1996 (Schmid et al.). Studies included in the meta analysis were all randomized, controlled trials with 10 or more patients receiving omeprazole plus antibiotics for at least 5 days and testing for *H. pylori* eradication at least 4 weeks after treatment. A total of 74 studies, involving 117 study arms and

4769 patients were identified. The eradication rate of *H. pylori* for each study arm was calculated by dividing the number of eradicated in each arm by the total number of patients randomized to that arm. The sample sizes and mean *H. pylori* eradication rates are presented in Table 4. Dual-therapy regimens consisting of omeprazole plus clarithromycin (OC), and omeprazole plus amoxicillin (OA) eradicated H. *pylori* infections 76% and 65% of the time, respectively, whereas, triple-therapy regimens with omeprazole, clarithromycin and amoxicillin (OAC) eradicated *H. pylori* 82% of the time (OAC vs. OA: $p<0.001$; OAC vs. OC: $p<0.001$). The triple-therapy regimen consisting of omeprazole, clarithromycin and amoxicillin was superior to dual-therapy regimens consisting of omeprazole and either clarithromycin or amoxicillin.

Table 4. Meta-regression analysis of 74 randomized controlled trials.

	OAC	**OC**	**OA**
Number of treatment arms	9	24	57
Number of patients	512	1021	2086
Eradication rate	82%	76%	65%

OAC = Omeprazole + Amoxicillin + Clarithromycin
OC = Omeprazole + Clarithromycin
OA = Omeprazole + Amoxicillin

Comment: Note studies included in the meta-analysis probably had variable OAC dose regimens, which might be different from the proposed oral regimen of the current application. Furthermore, this analysis compared arms across studies and contained studies from many regions which might have different eradication rates. However, these results are supportive of the randomized studies (studies 1 – 6) results.

3.1.5 Efficacy of Dual Therapy with Omeprazole and Amoxicillin (OA)

The review team has identified 3 US double-blind, controlled trials which evaluated omeprazole/amoxicillin dual therapy for the treatment of *H. pylori* eradication (Laine L, Johnson E. et al.). Studies I and II included patients with an active duodenal ulcer and Study III included patients with a documented history of duodenal ulcer. *H. pylori* eradication regimens in these 3 studies were omeprazole plus amoxicillin (OA) vs. omeprazole (O) vs. amoxicillin (A) for 2 weeks. Doses in Study I were omeprazole 40 mg b.d. and amoxicillin 500 mg t.d.s., and in Studies II and III they were omeprazole 20 mg b.d. and amoxicillin 1 g t.d.s. Patients were randomized to OA:O:A in a 2:1:1 ratio in Study I and in a 2:1:2 ratio in Studies II and III. Endoscopic biopsy tests (CLOtest, histological evaluation, and culture) were used for *H. pylori* diagnosis, and testing for *H. pylori* eradication was done at least 4 weeks after completion of therapy. Patients were considered to have persistent *H. pylori* infection if any single endoscopic biopsy test was positive at least 4 weeks after completion of therapy. *H. pylori* was considered to be eradicated if no test results were positive and at least two tests were negative. Subjects were included in the intent-to-treat (ITT) analysis if they were *H. pylori*-positive at baseline, took at least 1 dose of study medication, and in Studies I and II had a duodenal ulcer at baseline, and in Study III had a documented history of duodenal ulcer without active duodenal ulcer at baseline

endoscopy. Subjects from the ITT analysis were included in the Per Protocol (PP) analysis if they were compliant, did not receive prohibited medications, returned for the post-therapy endoscopy visit, and had no other significant illness as mentioned in the exclusion criteria.

Table 5 shows the intent-to-treat and per protocol results after therapy. *H. pylori* eradication was significantly greater with omeprazole/amoxicillin dual therapy than with either component monotherapy. OA dual therapy resulted in eradication rates of 39-46% in the ITT analyses and 46-54% in the PP analyses. Although omeprazole/amoxicillin dual therapy is significantly more effective than either omeprazole or amoxicillin monotherapy in curing *H. pylori* infection, the eradication rate is not greater than 50%.

Table 5. *H. pylori* Eradication Rates in 3 US Studies of Omeprazole and Amoxicillin

	Intent-to-Treat			**Per-Protocol**		
	OA	O	A	OA	O	A
Study I						
Number	72	33	37	54	25	19
Eradication rate	39%	3%	5%	50%	4%	11%
P-value	-	<0.05	<0.05	-	<0.05	<0.05
Study II						
Number	62	25	59	52	20	45
Eradication rate	40%	4%	5%	46%	5%	7%
P-value	-	<0.05	<0.05	-	<0.05	<0.05
Study III						
Number	48	29	50	37	22	39
Eradication rate	46%	0%	2%	54%	0%	0%
P-value	-	<0.05	<0.05	-	<0.05	<0.05

OA = Omeprazole + Amoxicillin
O = Omeprazole
A = Amoxicillin

3.2 Evaluation of Safety

Evaluation of safety is not applicable.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Not applicable.

4.2 Other Special/Subgroup Populations

None

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The efficacy of the proposed omeprazole plus amoxicillin plus clarithromycin triple-therapy (OAC) was examined by way of a review of published clinical data, focusing on a comparison of the triple-therapy co-packaged product to each pair of drugs (i.e., OAC vs. amoxicillin plus clarithromycin (AC), OAC vs. omeprazole plus clarithromycin (OC), OAC vs. omeprazole plus amoxicillin (OA)) in *H. pylori* eradication. A total of six randomized, comparative clinical trials were identified, out of which four (Studies 1, 2, 3, and 4) evaluated OAC versus AC, one (Study 5) compared OAC to OC, and one (Study 6) compared OAC to OA.

After 10 days of treatment in Studies 1, 2, and 3, the *H. pylori* eradication rates ranged from 69% to 83% for OAC triple-therapy vs. 32% to 37% for AC dual-therapy ($p<0.001$). In Study 4, *H. pylori* eradication rate was 94% for OAC triple-therapy and 26% for AC dual-therapy ($p<0.001$) after 7 days of treatment. These results show that the triple-therapy regimen consisting of omeprazole, amoxicillin, and clarithromycin was more efficacious in eradicating *H. pylori* than the dual-therapy with amoxicillin plus clarithromycin, demonstrating the large contribution of omeprazole to the triple therapy.

H. pylori eradication rate was 81.1% with OAC triple-therapy compared to 62.0% with OC dual-therapy ($p<0.001$) in Study 5 and 93% with OAC triple-therapy compared to 26% with OA dual-therapy ($p<0.001$) in Study 6. In addition, a meta-analysis of 74 studies reported dual-therapy regimens consisting of OC and OA eradicated *H. pylori* infections 76% and 65% of the time, respectively, whereas, triple-therapy OAC regimens eradicated H. *pylori* 82% of the time (OAC vs. OA: $p<0.001$; OAC vs. OC: $p<0.001$). Furthermore, three US double-blind, controlled trials demonstrated that dual therapy with OA is well tolerated but the *H. pylori* eradication rate which can be expected in the US is at best 50%. The triple-therapy regimen consisting of omeprazole, clarithromycin and amoxicillin was more efficacious in eradicating *H. pylori* than dual-therapy with either omeprazole plus clarithromycin, or omeprazole plus amoxicillin. The triple therapy results show a large contribution of clarithromycin to the regimen and a more modest contribution of amoxicillin.

These studies are limited by the fact that only 3 (Studies 1, 2, and 3) were conducted in the US and had the same oral regimen as the current application which is “Omeprazole Delayed-Release Capsules 20 mg plus Amoxicillin 1000 mg plus Clarithromycin 500 mg each given twice daily for 10 days”.

5.2 Conclusions and Recommendations

The efficacy of the proposed omeprazole plus amoxicillin plus clarithromycin triple-therapy (OAC) was examined by way of a review of published clinical data, focusing on a comparison of

the triple-therapy co-packaged product to each pair of drugs (i.e., OAC vs. amoxicillin plus clarithromycin (AC), OAC vs. omeprazole plus clarithromycin (OC), OAC vs. omeprazole plus amoxicillin (OA)) in *H. pylori* eradication. The triple-therapy regimen consisting of omeprazole, clarithromycin and amoxicillin was more effective in eradicating *H. pylori* than dual-therapy with either amoxicillin plus clarithromycin, or omeprazole plus clarithromycin, or omeprazole plus amoxicillin.

6. REFERENCES

Laine L, Suchower L, et al. Twice-Daily, 10-Day Triple Therapy with Omeprazole, Amoxicillin and Clarithromycin for *Helicobacter pylori* Eradication in Duodenal Ulcer Disease: Results of Three Multicenter, Douhle-Blind, United States Trials. *American Journal of Gastroenterology* 1998; 93:2106-12.

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Schmid CH, Whiting G, et al. Omeprazole Plus Antibiotics in the Eradication of *Helicobacter pylori* Infection: A Meta-Regression Analysis of Randomized, Controlled trials. *American Journal of Therapeutics* 1999; 6:25-36.

Laine L, Johnson E. et al. US Double-blind, Controlled Trials of Omeprazole and Amoxycillin for Treatment of Helicobacter pylori. Aliment Pharmacol Ther 1998; 12: 377-382.

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/

LAN ZENG
07/16/2010

KAREN M HIGGINS
07/16/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 50824 **Applicant: DAVA Pharmaceuticals** **Stamp Date: 6/19/2009**

Drug Name: Patient Compliance Pack consisting of Omeprazole Delayed-Release Capsules USP, 20 mg, Clarithromycin Tablets USP , 500 mg, and Amoxicillin Capsules USP, 500 mg

NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)		x		This is a 505(b)(2) application
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).			x	
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).			x	

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___N/A**_____**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

The sponsor is submitting this NDA as a 505(b)(2) application. The statistical section of the application is not sufficient for us to determine whether it is fileable. Regulatory will determine if the application is fileable.

This is a Patient Compliance Pack consisting of Omeprazole, Clarithromycin and Amoxicillin. The sponsor needs to determine the contribution of each of the components to the combination. A comparison of the combination to each of its components with the combination being superior to its components is required.

In addition, for a 505(b)(2) application, the sponsor is relying on previous information of each of the three drugs in the pack. Currently no such information is given in the application. It is not clear if all the necessary information for each of the three drugs in the pack will be available for review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.			x	
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.			x	
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			x	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			x	

Reviewing Statistician Date

Supervisor/Team Leader Date

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

/s/

HONGLING ZHOU
08/18/2009

KAREN M HIGGINS
08/19/2009