# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**050824Orig1s000**

# SUMMARY REVIEW

# Division Director Review #2

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|---|---|
| **Date** | February 8, 2011 |
| **From** | Renata Albrecht, MD |
| **Subject** | Review of NDA resubmission |
| **NDA/BLA #**<br>**Supplement#** | NDA 50-824 |
| **Pre-IND** | 101,174 |
| **Applicant** | DAVA Pharmaceuticals, Inc. |
| **Date of Submission** | September 21, 2009 (received September 22, 2009) |
| **Complete Response letter** | July 20, 2010 |
| **Resubmission Received** | December 7, 2010,<br>December 8, 2010 (Class 1, 2 months) |
| **Proprietary Name / Established (USAN) names** | No proprietary name approved;<br>Co-package of omeprazole delayed-release capsules, clarithromycin tablets, and amoxicillin capsules |
| **PDUFA Goal Date** | February 8, 2011 |
| **Dosage forms / Strength** | 20 mg omeprazole delayed-release capsules<br>500 mg clarithromycin tablets<br>500 mg amoxicillin capsules |
| **Proposed Indication(s)** | Treatment of *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence |
| **Treatment Regimen:** | Omeprazole 20 mg, clarithromycin 500 mg, amoxicillin 1000 mg given orally twice daily for 10 days |
| **Recommended:** | Approval |

**Material Examined:** Action package including reviews by

Project Management – Judit Milstein
CDTL – Joette Meyer (7/19/10, 2/8/11)
Clinical Pharmacology – Yori Harigaya, Philip Colangelo (7/16/10 and 2/8/11)
Microbiology – Anne Purfield, Shukal Bala (6/30/10 and 1/10/11)
Pharmacology/Toxicology – William Taylor (7/19/10 and 2/7/11)
Chemistry – Jeffrey Medwid, Steve Miller (7/8/10, 7/16/10, and 2/7/11)
Statistics – Lan Zeng, Karen Higgins (7/16/10 and 2/7/11)
OSE/DMEPA – Tara Turner, Zachary Oleszczuck, Denise Toyer, Carol Holquist, Karen Townsend (3/2/10, 7/13/10, 1/21/11 and 2/8/11)
DDMAC – Kathleen Klemm, Lisa Hubbard, Miahael Sauers, Sharon Watson, Wayne Amchin (7/1/10 and )
SEALD – Irisi Mascucci, Laurie Burke (7/16/2010)
Maternal Health Team – Richardae Araojo, Karen Feibus, Elizabeth Durmowicz, Lisa Mathis (6/2/10 and 2/xx/2011 )
Division of Gastrointestinal Products – Lara Dimick, Jugo Gallo-Torres, Andrew Mulberg (2/7/11)
Pediatric Review Committee (PeRC) Meeting – Lisa Mathis (1/26/2011)

# 1. Introduction

DAVA Pharmaceuticals Inc has submitted a 505(b)(2) application for a co-package containing a 10-day supply of omeprazole, clarithromycin, amoxicillin for the treatment and eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence. The co-package contains generic versions of each of three products:

| **Product and Strength** | **Application Number** | **Manufacturer** |
|---|---|---|
| Omeprazole Delayed-Release Capsule, 20 mg | ANDA 75-576 | Dr. Reddy Laboratories, Ltd. |
| Clarithromycin Tablet, 500 mg | ANDA 65-178 | Roxane Laboratories, Inc |
| Amoxicillin Capsule, 500 mg | ANDA 62-881 | DAVA Pharmaceuticals |

The proposed treatment regimen for the eradication of *H. pylori* infection and the treatment of duodenal ulcer disease (active or up to 1-year history) in adults is omeprazole capsule 20 mg, clarithromycin tablet 500 mg, plus amoxicillin capsules 1000 mg (2 capsules); these four pills are given twice daily for 10 days, in the morning and evening before eating a meal. They are provided in a box that contains 10 cards, one for each day, and the pills are blister-packed and marked as the morning dose (a sun symbol) and evening dose (a moon symbol).

The three drugs are generic versions of the following innovator or reference listed drug (RLD) products, which are cited by DAVA as supporting their application. These are generic products and no new preclinical or clinical studies were submitted. DAVA has not conducted any clinical studies with their co-package in *H. pylori* disease and is instead relying on the agency's previous findings of safety and effectiveness for this indication. Prilosec is a proton-pump inhibitor, Biaxin and Amoxil are antibiotics, and the three were approved to be used together for the indication of eradication of *H. pylori* as a regimen on June 30, 1998.

| **Product** | **Application Number** | **Manufacturer** |
|---|---|---|
| Prilosec® (omeprazole) | NDA 19-810 | Astra-Zeneca |
| Biaxin ® (clarithromycin) | NDA 50-662 | Abbott |
| Amoxil ® (amoxicillin) | ANDA 62-216 (NDA 50-459 was withdrawn) | GSK |

DAVA initially submitted their application June 18, 2009 but did not include a complete list of referenced drugs upon which they are relying. Following a teleconference with the FDA on August 14, 2009, DAVA was sent a letter September 15, 2009 that summarized the conference and outlined the steps that could be taken to correct the omissions. DAVA withdrew the application and resubmitted it September 21, 2009 citing the three products listed above.

After completing review of the application, DSPTP issued a Complete Response letter on July 20, 2010 because of outstanding labeling issues that had not been completed and because the application did not include a Pediatric Plan as required.

The applicant resubmitted the application on December 7, 2010 (received December 8, 2010) and it was classified as a Class 1 resubmisison (labeling only) with a 2 month review period; the PDUFA goal date is February 8, 2011.

## 2. CMC/Device

The CMC reviewer noted that all DMFs are acceptable, and Office of Compliance made an "acceptable" recommendation when all sites were inspected. EES has been addressed. Labeling, including, Carton and Container labeling, is acceptable.

## 3. Nonclinical Pharmacology/Toxicology

No new studies were submitted in the application. Labeling recommendations from Maternal Health were incorporated in the package insert. There are no outstanding issues from pharmacology/toxicology.

## 4. Clinical Pharmacology/Biopharmaceutics

There were no studies submitted for these generic drugs, labeling was updated to include information on drug-drug interactions. There are no outstanding issues from clinical pharmacology.

## 5. Clinical Microbiology

There were no studies submitted for these generic drugs. Labeling is acceptable and there are no outstanding issues from microbiology.

## 6. Clinical/Statistical- Efficacy

There are no new clinical trials submitted in this application. The applicant is relying on the agency's findings of safety and effectiveness for the innovator drugs, Priolosec®, Biaxin® and Amoxil® and the *H. pylori* indication previously granted in 1998. The applicant submitted literature references to demonstrate the contribution of each drug component to the treatment effect, in keeping with the principles of the fixed combination drug regulation: 21 CFR 300.5. These references were examined and the findings summarized in the initial statistical review (O=omeprazole, C=clarithromycin, A=amoxicillin):

> 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 metaanalysis 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 analyses support the contribution of each component to the treatment regimen by showing that the triple regimen is superior to each of the dual components, and addresses the Division's request. Labeling is acceptable.

## 7. Safety

There was no safety information submitted. The applicant is relying on the findings of safety and effectiveness from the three approved products, and the approved indication. As noted

above, the co-package contains three generics each of which relies on a reference listed drug for its labeling.

## 8. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

## 9. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Based on emails from Oluchi Elekwachi of the Pediatric and Maternal Health Staff, this co-package represents a new ingredient under PREA, as determined by Rosemary Addy.

The applicant submitted a proposed justification (b) (4) of pediatric studies in the original application; the justification was found inadequate. A request for a new pediatric development plan was sent October 26, 2009, and the applicant submitted a revised pediatric plan on January 18, 2010. Their justification was considered inadequate because of the reasons enumerated below and communicated to DAVA in the FDA May 11, 2010 letter that again requested a revised pediatric drug development plan:

(b) (4)

(b) (4)

The applicant was advised that a Pediatric Plan is required during the review process and also in the Complete Response letter dated July 20, 2010, and DAVA included a pediatric plan in the resubmission. However,), there is currently no treatment for *H. pylori* approved in pediatric patients and DSPTP recommends that a regimen of a PPI such as omeprazole (or esomeprazole) and antibiotics amoxicillin and clarithromycin would be appropriate to consider for development because there is already pediatric experience with these PPIs in pediatric

patients and the two antibiotics are also used in pediatrics. Therefore, DSPTP consulted with the MHT and the Division of Gastrointestinal Products (DGP) regarding the study of *H pylori* in pediatric patients and preparation of material for PeRC. In addition, there was extensive , discussion of this topic and drug development at the January 26, 2011 PeRC meeting. The discussion included a fairly extensive discussion on the rarity of ulcer disease in pediatric patients and the likely challenge of conducting a study in pediatric patients. Children 0-2 years of age have been waived because the disease essentially is not seen in this age group and patients from 2 to less than 17 years of age are being deferred, recognizing that even a study in this age group may take a long time or ultimately not be feasible because of uncommon diagnosis of *H. pylori* with peptic ulcer. (b) (4) Finally, there are no data on the safety of the three products (omeprazole, clarithromycin, amoxicillin in pediatric patients.) On the other hand, there are pediatric formulations, including some generic formulations, available for each of these products; therefore development of pediatric formulations will not be a limiting factor in evaluating this treatment regimen.

All the products contained in the OCA co-packaged product are approved in pediatric patients 2 years to less than 17 years for different indications and the safety profiles of the products are well characterized at the approved dosing. When the dosing regimen for the clinical trial of the treatment of *H. pylori* in pediatric patients is determined, the need for additional PK data on the individual components will be determined.

Although the company submitted a proposal to (b) (4) (b) (4) Instead DSPTP proposes to ask for a non-comparative clinical study to evaluate safety and efficacy, and also to issue a Pediatric Written Request to DAVA as well as the sponsors of omeprazole/Prilosec and esomeprazole/Nexium (AstraZeneca). PeRC concurred with the Divisions approach.

A brief synopsis of the study proposed by DSPTP is included below:

> Single arm safety and efficacy study of OCA for eradication of *H. pylori* infection in pediatric patients, ages 2 to less than 17 years, with active or a 1-year history of duodenal ulcer disease
>
> > *Note: H. pylori causes a luminal infection of the stomach and duodenum. Eradication of infection is felt to be secondary to the effects of high, local concentrations of antimicrobials in the GI tract and is not thought to be related to systemic exposures. Therefore, it is believed that pediatric dosing information cannot be obtained by simply comparing systemic exposures in adults.*
>
> A sample size of 78 patients treated with the OCA regimen gives 80% power to rule out an unacceptable eradication rate of 60% or less using a two sided type I error rate

of 0.05 and assuming a true eradication rate of 75%. Because the untreated eradication of *H. pylori* in adults is approximately 0%, the results seen in the treated patients can be attributed to the treatment regimen, and not spontaneous resolution of the disease.

**Entry criteria:**
Inclusion criteria:

- Symptomatic patients undergoing a clinically indicated endoscopy found to have *H. pylori* infection and endoscopically proven duodenal ulcer disease

Exclusion criteria:

- Patients with secondary ulcers, e.g. secondary to stress, drug related
- History of any previous esophageal or gastric surgery, except for simple closure of perforated ulcer.
- Gastric outlet obstruction.
- Hypersecretory states, such as Zollinger-Ellison Syndrome.

Presence of both active gastric and duodenal ulcers, or presence of three or more active ulcers. Multiple ulcers are believed to potentially signify disease of other etiology (e.g., undiagnosed Zollinger-Ellison Syndrome

**Clinical endpoints:**

- The primary efficacy endpoint should be eradication of *H. pylori* measured at least 28 days, but no more than 56 days from the end of the treatment.

- For definition of eradication of *H. pylori* by diagnostic see Table 2, in Appendix of the draft Guidance for Industry: *Helicobacter pylori*-Associated Duodenal Ulcer Disease in Adults: Developing Drugs for Treatment.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184500.pdf

*Of note, the Guidance provides for the use of a UBT in place of endoscopy at the test-of-cure visit. If the test is negative no further testing is needed. However, if the test is positive the patient should undergo endoscopy.* (b) (4) [redacted]

The company was contacted and advised that a written request will be issued and that the expectation for the protocol and timelines for completing the study and PREA requirements are as follows; the company acknowledged the information:

a. *Protocol Submission: February 28, 2012*
b. *Study Completion: February 28, 2018*
c. *Study Submission: February 28, 2019*

## 10. Other Relevant Regulatory Issues

The 505(b)(2) application was granted clearance on July 6, 2010 by the Office of New Drugs. (Kim Quaintance) and again on January 8, 2011 (Beth Duvall Miller per Judit Milstein).

## 11. Labeling

**Proprietary Name**
The applicant submitted multiple trade names to date (b) (4) (b) (4) DDMAC has found some names promotional The company refers to the product as TTNB (Triple Therapy Brand Name) in the absence of an approved trade name. Absence of a trade name does not preclude approval, and a statement regarding trade name review will be included in the Approval Letter.

**Consults on PLR Package Insert**
Recommendations made by the review team, DDMAC, Maternal Health Staff (MHS), and SEALD have been incorporated in the revised labeling and accepted by the applicant.

The applicant also requested to omit the phrase regarding patients with ulcers who should receive an "additional 18 days of omeprazole 20 mg once daily" from the DAVA package insert. However, as noted by Dr Meyer, DAVA is relying on the findings of safety and efficacy based on the studies done for Prilosec and therefore the DAVA labeling needs to include the complete information based on those findings. In contrast the applications cited by DAVA as precedents for Prevacid and PrevPac did not include additional lansoprazole dosing and their labeling is different. It was unclear why the company wished to omit the 18 days statement (b) (4) However, given that the application relies on the approved regimen as demonstrated for Prilosec, the language needs to be consistent with the PRILOSEC language provided below. The company agreed with this language and included it in their Febuary 3, 2011 package insert submission.

> *Triple Therapy (omerprazole/clarithromycin/amoxicillin)* — The recommended adult oral regimen is omeprazole 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omerprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

**Carton and Immediate Container Labels**
DMEPA and CMC have made recommendations to the carton and container labeling which have been accepted by the applicant.

# 12. Recommendations/Risk Benefit Assessment

This 505(b)(2) application relies on the agency's findings of safety and effectiveness for approval of the *H. pylori* treatment indication for this co-packaged product. The statistical reviewer summarized the contribution of the components to the treatment effect, and these three products have been approved/ marketed individually since 1998 for this indication. The co-package provides a new presentation for three generic products to be marketed in one package for the indication, and also will provide for one package insert that is focused on this indication and does not include the other indications for which the individual products are approved. The three drugs are in a blister package and each days regimen is on a separate card; there are a total of 10 cards for the complete regimen.

In the December 7, 2010 resubmission, DAVA addressed the outstanding deficiencies from the July 20, 2010 Complete Response Letter:

- Revised labeling (package insert, color carton/container labeling) for the co-package.
- Amoxicillin labeling (package insert) so that the description of the amoxicillin capsules can be compared to the one to be included in the co-package.
- Pediatric drug development plan – (b) (4) (b) (4) All three of these products are individually approved and have been used individually for other indications in pediatric patients, thus their individual safety profiles in pediatric patients are characterized. In addition, each of the products is available in liquid formulation that could be used in younger patients, thus a formulation could be made available. Therefore, OCA should be evaluated in pediatric patients for *H. pylori* disease. This matter was discussed with PeRC on January 26, 2011, following initial discussions with DGP and Maternal Health Team. The decision was to waive pediatric studies in the 0-2 year age group and defer studies in the 2 to less than 17 year age group, and a PWR issued to DAVA and PPI companies (for omeprazole, esomeprazole). Recognizing that *H pylori* is not very frequent in pediatrics, a non-comparative design in 78 patients is proposed and should this trial become unfeasible, the matter can be revisited. (b) (4)

The applicant has addressed all the deficiencies. All consultant recommendations have been addressed and/or incorporated in labeling and all review disciplines have recommended approval. The only exception is that to date none of the proposed proprietary names proposed by the company have been found acceptable by DMEPA, however, the NDA can be approved without a proprietary name.

The applicant will be issued an **Approval letter** for this application, including a paragraph waiving the ½ page limit for the Highlights section of labeling

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/s/

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RENATA ALBRECHT
02/08/2011