

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**050824Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

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| <b>Date</b>  | February 8, 2011   |
| <b>From</b>  | Joette M. Meyer, Pharm.D.  |
| <b>Subject</b>                                     | Cross-Discipline Team Leader Review  |
| <b>NDA/BLA #</b>                                   | NDA 50-824   |
| <b>Supplement#</b>                                 |  |
| <b>Applicant</b>                                   | DAVA Pharmaceuticals, Inc.   |
| <b>Date of Re-Submission</b>                       | December 8, 2010   |
| <b>PDUFA Goal Date</b>                             | February 8, 2011   |
|  |  |
| <b>Proprietary Name / Established (USAN) names</b> | No proprietary name approved; co-package of three drugs: Omeprazole Delayed-Release Capsules USP 20 mg; Clarithromycin Tablets USP, 500 mg; and Amoxicillin Capsules USP, 500 mg   |
| <b>Dosage forms / Strength</b>                     | omeprazole delayed-release capsules 20 mg<br>clarithromycin tablets 500 mg<br>amoxicillin capsules 500 mg  |
| <b>Proposed Indication(s)</b>                      | Treatment of <i>H. pylori</i> infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate <i>H. pylori</i> . Eradication of <i>H. pylori</i> has been shown to reduce the risk of duodenal ulcer recurrence |
| <b>Recommended:</b>                                | Approval   |

### 1. Introduction

This submission contains a co-package consisting of omeprazole delayed-release capsules USP, 20 mg, clarithromycin tablets USP, 500 mg, and amoxicillin capsules USP, 500 mg (OCA) packaged in blister cards for 1 full day of treatment and then put in cartons containing 10 one day blisters. A ten day supply is intended 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.

Each of these three 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 (FDCA), certain drug approvals can rely on literature or on an Agency finding of safety and/or effectiveness for an approved drug product.

The original NDA, submitted under section 505(b)(2) of the Food Drug and Cosmetic Act on September 21, 2009 (received September 22, 2009), was issued a Complete Response letter on July 20, 2010. The noted deficiencies were as follows:

#### PEDIATRIC PLAN

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.

The proposed pediatric plan included in your original submission contained a request and justification (b) (4) of pediatric studies for your co-packaging of omeprazole/clarithromycin/amoxicillin product. Your justification (b) (4) was found inadequate and on October 26, 2009, we issued correspondence requesting that you submit a revised pediatric plan, and included a description of the type of justification needed to waive and/or defer pediatric studies. This correspondence also requested that you respond by November 30, 2009.

You provided a revised pediatric plan on January 18, 2010 that contained a second request and justification (b) (4) of pediatric studies in patients (b) (4). We did not agree with your justification; therefore on May 11, 2010, we issued a correspondence requesting the submission of a revised pediatric plan. In this request, we noted there is currently no approved therapy for the treatment of pediatric patients with *H. pylori* infection and duodenal ulcer disease; therefore, we asked that you submit a revised pediatric plan that outlines the proposed pediatric studies and the development of an age-appropriate formulation, with inclusion of the timeline for completion of such studies. We asked that this information be submitted by June 7, 2010. As of the date of this letter, we have not received your revised pediatric plan.

To address this deficiency, please, submit your pediatric drug development plan along with a request for deferral of pediatric studies as requested in our correspondence of May 11, 2010. The pediatric development plan is for the indication of 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.

#### **LABELING**

We have reviewed the labeling of your product, including package insert, and carton and container labeling. Before we can approve your application, you will need to submit the following labeling information:

1. Submit draft labeling (package insert) that incorporates revisions described in the attached labeling (package insert). In addition, submit updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.
2. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.
3. Submit draft color copies of carton and container labeling revised as described in our correspondence dated July 6, 2010. A copy of this correspondence is attached to this letter.
4. Submit labeling (package insert) for the amoxicillin capsules, ANDA 62-881, that you intend to use in your co-packaged product, so that we may compare the description of the amoxicillin in the ANDA with the description in your co-package product.

On December 8, 2010 the applicant responded to the Complete Response letter with a Class 1 Resubmission. The application contains a Pediatric Plan, a revised package insert in PLR format, proposed carton and container labeling, and the approved package insert for amoxicillin capsules (ANDA 62-881). There are no new non-clinical or clinical trials included in the submission. The applicant previously referenced the findings of safety and effectiveness of three Reference Listed Drugs, Prilosec® (omeprazole delayed-release capsules), Biaxin® (clarithromycin tablets), and Amoxil® (amoxicillin capsules).

## **2. Background**

See CDTL review of the original NDA submission.

## **3. CMC/Device**

See previous CMC review by Jeffrey Medwid, PhD entered into DARRTS on July 8, 2010 and addendum on July 16, 2010 acknowledging all inspections are complete and found to be acceptable. All labeling issues, including the carton and container, were found acceptable on February 7, 2011, as noted in Dr. Medwid's review.

## **4. Nonclinical Pharmacology/Toxicology**

No new information was provided. See previous Pharmacology/Toxicology review by William Taylor, PhD entered into DARRTS on July 19, 2010 and February 7, 2011.

## **5. Clinical Pharmacology/Biopharmaceutics**

The Clinical Pharmacology team made revisions to the proposed OCA package insert by including additional information on drug interactions with omeprazole, as recommended in a consult review from the Division of Gastroenterology Products (see review by Dr. Lara Dimick entered into DARRTS on February 7, 2011). See Clinical Pharmacology reviews by Yori Harigaya, PhD entered into DARRTS on July 16, 2010 and February 8, 2011.

## **6. Clinical Microbiology**

No new microbiology data was provided. The microbiology team agrees with the applicant's proposed package insert, with respect to the microbiology sections (12.1 and 12.4). See Microbiology reviews by Anne Purfield, PhD entered into DARRTS on June 30, 2010 and January 10, 2011.

## **7. Clinical/Statistical - Efficacy**

No new clinical trial data was submitted. See Statistical reviews entered into DARRTS by Lan Zhang, PhD on July 16, 2010 and February 7, 2011.

## 8. Safety

There was no safety review conducted. The applicant is relying on the findings of safety and effectiveness from the three approved products.

## 9. Financial Disclosure

As there were no clinical studies submitted with this application, no financial disclosures were reviewed.

## 10. Advisory Committee Meeting

No Advisory Committee meeting was held for this application.

## 11. 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.

See CDTL review of the original application regarding communications between FDA and the applicant regarding their request and justification [REDACTED] (b) (4) of pediatric studies, which were not agreed upon. The current submission contains revised Pediatric Plan which includes a request for deferral of pediatric studies for patients [REDACTED] (b) (4) 17 years of age.

[REDACTED] (b) (4)  
[REDACTED] he

applicant proposes a partial waiver for pediatric studies in patients from birth to <2 years of age and a deferral of the older age groups. Their Pediatric Plan consists of a trial in pediatric patients 2 to 17 years of age to compare the [REDACTED] (b) (4)

[REDACTED] profile of omeprazole, clarithromycin, and amoxicillin administered individually as reported in the approved ANDAs for the respective products. They propose to use FDA-approved, commercially available powders for suspension to conduct the trial and commits to work to develop a co-package of these suspensions.

[REDACTED] (b) (4)  
[REDACTED] (b) (4)  
[REDACTED] (b) (4)

The Division did not agree with the applicant's proposal to conduct a PK study in patients 2 to 17 years, since *H. pylori* causes a luminal infection in 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. (b) (4) the Division would like to request a single-arm clinical efficacy trial in 78 pediatric patients with *H. pylori* and current or a history of duodenal ulcer to establish the appropriate safe and effective dose of OCA in children. The application was discussed with the Pediatric Review Committee (PeRC) on January 26, 2011. Background documents for the meeting were prepared by Dr. Elizabeth Durmowicz from the Pediatric and Maternal Health Staff with input from DSPTP (see completed PREA Waiver/ Deferral Request template in DARRTS). The committee agreed to the Division's request for a waiver of pediatric studies in patients aged 0 to 2 years and a deferral in patients aged >2 to 17 years. There was discussion of the feasibility of finding enough children with duodenal ulcers to be able to complete the trial, but it was decided that the applicant would be asked to make an attempt and that a waiver could be reconsidered in the future if enrollment was lower than expected. (b) (4)

## 12. Other Relevant Regulatory Issues

During review of the original submission, the Division requested clearance of the application for action from a 505(b)(2) perspective by the (b)(2) review staff in the Immediate Office, Office of New Drugs. The application was granted clearance on July 6, 2010 (email, Kim Quaintance). The Division again requested clearance from OND for the re-submitted application, which granted in an email from Beth Duvall-Miller on January 18, 2011.

## 13. Labeling

### Proprietary Name

The applicant has made three attempts to submit a proprietary name in the last review cycle. All three names were found to be unacceptable by DMEPA (see original CDTL review). In the current review cycle the applicant submitted the name (b) (4) which was also found to be unacceptable to DMEPA and was communicated to the applicant during a teleconference on January 11, 2011. DMEPA asked the applicant to submit three additional proposed names. On January 19, 2011 the applicant submitted the names (b) (4) (which was found not acceptable by DDMAC), (b) (4) (both of which were cleared by DDMAC, but found to be unacceptable by DMEPA); email summarizing the status of these three names sent by Karen Townsend dated February 3, 2011. DMEPA will follow-up with the applicant regarding the acceptability of their proposed proprietary names after the action date. The product can be approved without a proprietary name.

### Consult on PLR Package Insert

The Division consulted the Division of Gastroenterology Products to review the proposed package insert for OCA to evaluate if it is consistent with the approved labeling for omeprazole and lansoprazole. A consult for omeprazole was prepared by Dr. Lara Dimick (entered into DARRTS on February 7, 2011) which stated that, in general, the OCA label covered all the information in the most current version of the omeprazole label and was adequately organized. However, she requested a few additions/revisions:

#### Highlights:

- Include additional drug-drug interactions to the Drug Interactions section that are also mentioned in Section 7 of the full prescribing information
- Add the interaction with cilostazol to the Drug Interactions section
- Include mention of use in hepatic impairment and Asian patients to the Use in Specific Populations section

#### Full Prescribing Information

- Add a new subsection in Warnings and Precautions on “Combination Use of Omeprazole with Clarithromycin”
- Add a new subsection in Drug Interactions describing the interaction with cilostazol
- Add two new subsections to Use in Specific Population on use in Hepatic Impairment and Asian Populations
- Revise the introductory paragraph in the Clinical Pharmacology, Pharmacokinetics subsection to be consistent with information in the “Combination Therapy with Antimicrobials” subsection

The CDTL and Clinical Pharmacology Team agreed with the above requests and revised the package insert, with the exception of the request to add a new subsection in Warnings and Precautions.

**CDTL Comment:** The requested additions to Warnings and Precautions section was the following:

*Co-administration of omeprazole and clarithromycin has resulted in increases in plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin. [See **Clinical Pharmacology (12)**]*

*Concomitant administration of clarithromycin with cisapride or pimozide is contraindicated.*

The information on plasma levels was not added because omeprazole and clarithromycin are indicated for use (in combination with amoxicillin) for the treatment of *H. pylori* infection. It is not clear what the clinical significance of increased plasma concentrations of omeprazole, clarithromycin, and 14-hydroxyclearithromycin is when the drugs are used together treat *H. pylori*. However, the combination has been found to be safe and effective.

Cisapride is no longer marketed in the US so the Division removed reference to it in the package insert. The interaction with pimozide is already noted in the Contraindications section.

### **Carton and Immediate Container Labels**

The Division consulted DMEPA for evaluation of the carton and immediate container labels to identify areas that could contribute to medication errors.

DMEPA's comments on the carton and container labels in the original submission were sent to the applicant by the Division in a fax dated July 6, 2010 but were not returned prior to the Complete Response letter issuing. Revised carton and container labels were included in the re-submission. The majority of the revisions were satisfactory (See DMEPA review by Lubna Merchant, entered into DARRTS on January 21, 2011), but a few additional comments on the Patient Card were sent to the applicant on January 27, 2011. The applicant submitted revised labeling on February 3, 2011 which was found to be acceptable.

### **Package Insert**

The submission contained a proposed package insert which incorporated the recommended changes, as noted in the Complete Response letter of July 20, 2011. Additional edits were made, as noted above based on feedback from DGP. Of note the applicant requested omission of wording in Section 2 "Dosage and Administration" referring to the additional 18 days of treatment with omeprazole following 14 days of OCA in patients with an active ulcer, as it is not consistent with the package insert for Prevacid® (co-package of lansoprazole, clarithromycin, and amoxicillin). The following justification for including this wording the OCA labeling was sent to the applicant on February 1, 2011:

As noted in the Clinical Studies section of the omeprazole package insert: Patients randomized to Studies 1 and 2 (i.e., patients with an active duodenal ulcer) who were also randomized to OCA "also received an additional 18 days of PRILOSEC 20 mg once daily." As you note in your submission, the following wording accompanies the *H. pylori* indication in the omeprazole label and describes how the drugs were administered to patients in the clinical studies:

*Triple Therapy (PRILOSEC/clarithromycin/amoxicillin) — The recommended adult oral regimen is PRILOSEC 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 PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.*

The lansoprazole clinical studies which supported approval of Prevacid and Prevacid for the *H. pylori* indication were not conducted with additional lansoprazole after the initial 10 or 14 days of treatment.

Therefore, as you are relying on the findings of safety and effectiveness from the omeprazole NDA, the labeling for OCA must discuss how the trials leading to approval were conducted.

The applicant agreed to include the wording, accepted all other changes and submitted a final version of the package insert which was found to be acceptable on February 3, 2011.

## **14. Recommendations/Risk Benefit Assessment**

The CDTL recommends approval of the re-submission. The review team agrees with this intended action.

No REMS are required.

No Postmarketing Requirements or Commitments have been identified.

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/s/  
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JOETTE M MEYER  
02/08/2011