CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050824Orig1s000

MEDICAL REVIEW(S)

Division Director Review

Date	July 20, 2010
From	Renata Albrecht, MD
Subject	Review of NDA
NDA/BLA # **Supplement#**	NDA 50-824
Applicant	DAVA Pharmaceuticals, Inc.
Date of Submission	September 21, 2009 (received September 22, 2009)
PDUFA Goal Date	July 22, 2010
Proprietary Name / **Established (USAN) names**	No proprietary name approved; Co-package of omeprazole delayed-release capsules, clarithromycin tablets, and amoxicillin capsules
Dosage forms / Strength	20 mg omeprazole delayed-release capsules 500 mg clarithromycin tablets 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:	Complete Response pending Labeling and a Pediatric Drug Development Plan

Material Examined: Action package including reviews by

CDTL – Joette Meyer (7/19/10)
Clinical Pharmacology – Yori Harigaya, Philip Colangelo (7/16/10)
Microbiology – Anne Purfield, Shukal Bala (6/30/10)
Pharmacology/Toxicology – William Taylor (7/19/10)
Chemistry – Jeffrey Medwid, Steve Miller (7/8/10, 7/16/10)
Statistics – Lan Zeng, Karen Higgins (7/16/10)
OSE/DMEPA – Tara Turner, Zachary Oleszczuck, Denise Toyer, Carol Holquist (3/2/10, 7/13/10)
DDMAC – Kathleen Klemm, Lisa Hubbard, Miahael Sauers, Sharon Watson, Wayne Amchin (7/1/10)
Maternal Health Team – Richardae Araojo, Karen Feibus, Lisa Mathis (6/2/10)

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.

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 issues for the package insert and carton/container need to be resolved before the application can be approved.

3. Nonclinical Pharmacology/Toxicology

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

4. Clinical Pharmacology/Biopharmaceutics

There were no studies submitted for these generic drugs. Other than labeling, there are no outstanding issues from clinical pharmacology.

5. Clinical Microbiology

There were no studies submitted for these generic drugs. Other than labeling, 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 was asked to submit 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 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.

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) waiver 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)

As of the date of this review, the applicant has not submitted a revised pediatric drug development plan. Approval cannot be granted in the absence of a pediatric plan.

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).

11. Labeling

Proprietary Name

The applicant submitted three trade names to date (b) (4) 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.

Consults on PLR Package Insert

Recommendations made by DDMAC, Maternal Health Staff (MHS), and SEALD have been incorporated in the revised labeling to be sent to the applicant.

Carton and Immediate Container Labels
DMEPA and CMC have made recommendations to the carton and container labeling which were sent to the applicant on July 6, 2010. The applicant has not responded to date.

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.

However, before the application can be approved, the company will need to submit

- 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.
- (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.

The applicant will be issued a Complete Response letter requesting a revised pediatric plan, as well as revised labeling for the co-package, and for the amoxicillin generic (to compare description and appearance of the capsule).

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

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

/s/

RENATA ALBRECHT
07/20/2010

Cross-Discipline Team Leader Review

Date	July 15, 2010
From	Joette M. Meyer, Pharm.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 50-824
Applicant	DAVA Pharmaceuticals, Inc.
Date of Submission	September 22, 2009
PDUFA Goal Date	July 22, 2010
Proprietary Name / Established (USAN) names	No proprietary name approved; Co-package of omeprazole delayed-release capsules, clarithromycin tablets, and amoxicillin capsules
Dosage forms / Strength	20 mg omeprazole delayed-release capsules 500 mg clarithromycin tablets 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
Recommended:	Complete Response pending Labeling and a Pediatric Drug Development Plan

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.

There are no new studies included in the submission, the applicant is referencing the findings of safety and effectiveness of three Reference Listed Drugs, Prilosec® (omeprazole delayed-release capsules), Biaxin® (clarithromycin tablets), and Amoxil® (amoxicillin capsules).

The applicant submitted an NDA under section 505(b)(2) of the FDCA on June 18, 2009 (received June 19, 2009). The filing date for the application was August 18, 2009.

The cover letter accompanying the 505(b)(2) application stated:

> "…the basis for submission for this 505(b)(2) NDA is the FDA-approved labeling for Omeprazole Delayed-Release Capsules USP, 20 mg, which specifies the use of triple therapy (omeprazole, clarithromycin and amoxicillin) 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. DAVA's proposed Physician's Insert (Content of Labeling) was prepared based upon the currently approved labeling for each of the three (3) ANDA approved finished drug products which are the component products of DAVA's Patient Compliance Pack, as well as recommendations provided by the Agency."

A teleconference between the applicant and representatives from the Division of Special Pathogen and Transplant Products, Office of Antimicrobial Products, Office of New Drugs, and Office of Regulatory Policy occurred on August 14, 2009, notifying the applicant of deficiencies identified in the application.

The following is a summary of the deficiencies discussed during the teleconference, as taken from the minutes of the meeting (entered into DARRTS September 15, 2009):

1. DAVA's NDA 50-824 was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), and this proposed co-packaged product is composed of 3 drug products that have been approved in ANDAs. Based on this submission, it appears that DAVA intends to rely upon the Agency's finding of safety and effectiveness for each of the reference listed drugs (RLDs) that were the basis for submission of each of the ANDA products in the proposed co-packaged product. However, DAVA's submission does not identify these RLDs as the listed drugs relied upon for its 505(b)(2) application.

2. A 505(b)(2) application contains "full reports of investigations" of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. Accordingly, reliance only on the approved ANDAs is not acceptable to support your proposed 505(b)(2) application. DAVA would need to identify the NDA product that was the basis for submission (the RLD) for each of the ANDA products in the proposed co-packaged product as the listed drugs relied upon to support its proposed 505(b)(2) application.

3. DAVA identified "Prilosec® Content of Labeling" on Form 356h as the listed drug relied upon for this 505(b)(2) application. Although DAVA indicated during the teleconference that they believed they had identified Prilosec as a listed drug relied upon for this 505(b)(2) application, FDA noted that this was unclear (especially in light of the paragraph I certification which is inconsistent with the multiple unexpired patents listed in the Orange Book for NDA 19-810 for Prilosec). FDA advised that DAVA had not identified a listed drug relied upon for the clarithromycin and amoxicillin components of this proposed co-packaged product.

4. If DAVA intends to seek approval for a co-packaged product composed of Omeprazole Delayed-Release Capsules 20 mg, Clarithromycin Tablets, 500 mg, and Amoxicillin Capsules, 500 mg, in reliance on the Agency's finding of safety and effectiveness for the NDA products upon which the ANDA approvals were based, DAVA would need to identify each of the RLDs for the ANDAs as listed drugs relied upon and provide an appropriate patent certification or statement for each patent listed in the Orange Book or each listed drug relied upon. However, we interpret section 505(b)(4)(A) of the FDCA, added by the Medicare Modernization Act (MMA), to preclude a 505(b)(2) applicant from amending or supplementing a 505(b)(2) application to seek approval of a drug that relies on the Agency's finding of safety and effectiveness for a drug that is different from the drug identified in a previous submission of the application. Accordingly, the identification of additional listed drugs relied upon is not the type of

change that may be made in an amendment to a 505(b)(2) application. DAVA may elect to withdraw and resubmit its 505(b)(2) application to identify each of the RLDs for the ANDA products as listed drugs relied upon in support of its 505(b)(2) application.

5. DAVA noted that they believed they had adequately identified Prilosec as a listed drug relied upon, and inquired whether an amendment to identify two additional listed drugs relied upon would be precluded by section 505(b)(4)(A) of the FDCA. FDA noted that it does not currently interpret section 505(b)(4)(A) to permit such an amendment, and referred DAVA to the citizen petition response regarding venlafaxine (Docket No. FDA-2008-P-0329), specifically footnote 30 on page 16.

6. With respect to Prilosec, which was not clearly identified as a listed drug relied upon, we noted that a paragraph I certification would not be an acceptable patent certification because there are several unexpired patents listed in the Orange Book for NDA 19-810. Thus, DAVA would have the option of submitting a paragraph III certification, paragraph IV certification, or, if method-of-use patents were identified in the Orange Book, a 505(b)(2)(B) statement.

In response to the teleconference, the applicant withdrew the NDA on August 20, 2009 (after the application had been filed).

The applicant resubmitted the NDA under section 505(b)(2) of the FDCA on September 21, 2009 (received September 22, 2009) with revised Listed Drug information. The application was filed on November 22, 2010 and given a Standard priority.

2. Background

FDA approved *H. pylori* treatment regimens are shown in Appendix 1. OCA, consisting of the three drugs dispensed individually, was approved on June 30, 1998.

Helidac® is a co-package of bismuth subsalicylate, metronidazole, and tetracycline hydrochloride, approved as a 505(b)2 NDA on August 15, 1996. Helidac is to be taken with a H_2-blocker, which is not part of the co-package.

Lansoprazole, clarithromycin, and amoxicillin (LCA) is marketed as the individual components and also as a co-packaged blister pack (PREVPAC®), which was approved on December 2, 1997.

Pylera® a fixed combination capsule of bismuth subcitrate potassium, metronidazole and tetracycline hydrochloride was approved on September 28, 2006 and is prescribed with omeprazole, which is marketed separately.

3. CMC/Device

According to the CMC reviewer, the NDA is submitted for approval of a co-package consisting of omeprazole delayed-release capsules USP, 20 mg, clarithromycin tablets USP, 500 mg, and amoxicillin capsules USP, 500 mg. All three Active Pharmaceutical Ingredients (APIs) are prepared and released according to either an approved ANDA (clarithromycin) or

acceptable DMFs (amoxicillin and omeprazole) as listed in section 17 of the Chemistry Review Data Sheet. All API's are USP grade material. The specification for all three API's are at least as tight as the approved USP specifications listed in the current USP and are the subject of currently active ANDAs. Consequently no recommendations will be made to the API manufacturers to tighten specifications.

The three APIs are then manufactured and released under approved ANDAs as listed in section 17 of the Chemistry Review Data Sheet. The specification for all three drug products including omeprazole delayed-release capsules USP, 20 mg, clarithromycin tablets USP, 500 mg, and amoxicillin capsules USP, 500 mg are at least as tight as the approved USP specifications listed in the current USP and are the subject of approved ANDA's. Consequently no recommendations will be made to the drug product manufacturers to tighten specifications.

The three drug products are then shipped to (b) (4) (b) (4) for the purpose of packaging the component products into blister packs and cartons.

The stability testing of the blister-packed product was conducted by (b) (4) (b) (4)

Sufficient information is available on raw material controls, manufacturing processes and process controls, and specifications for assuring consistent product quality of the drug substances and drug product. The NDA also has provided sufficient stability information on the three dosage forms blister-packed together to assure strength, purity, and quality of the drug product during the expiration dating period.

Acceptable resolution of labeling of both the insert and carton labeling still need to be completed. Recommendations regarding the blister and carton labels and the package insert were sent to DAVA on July 6, 2010.

A Pre-Approval Inspection of (b) (4) (b) (4)) was conducted by (b) (4) in (b) (4), and a 483 was issued. Follow-up responses from (b) (4), dated (b) (4) satisfied all of the concerns for the 483 and the laboratory was deemed acceptable.

Several manufactures of the drug substances and finished dosages were inspected by the Office of Compliance and found to be acceptable. However, as of July 8, 2010, the Office of Compliance had not provided a final recommendation in EES on the overall acceptability of the inspections.

Therefore, in the CMC review dated July 8, 2010, the CMC reviewer is not recommending approval until the following issues are resolved:

1. Acceptable Inspections of all sites added into EES. At the time of this review, July 8, 2010, all sites have been found acceptable and reported in EES as such except (b) (4)

(b) (4) The inspection has been completed. Documentation and final recommendation into EES has not been completed.

2. Acceptable resolution of labeling of both the insert and carton labeling still need to be completed. Recommendations regarding the blister and carton labels and the package insert were sent to DAVA on July 6, 2010.

CDTL Reviewer's Comment: On July 12, 2010, the CMC reviewer forwarded an email from the Office of Compliance which contained the final acceptable recommendation from EES for this NDA.

The CMC review was amended by Jeffrey Medwid, PhD and entered into DARRTS on July 16, 2010 and acknowledged that all inspections were complete and found to be acceptable. The revised CMC recommendations are as follows:

An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.

3. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology data was included in the application. The applicant has referenced the findings of safety and efficacy for the Reference Listed Drugs Prilosec® (omeprazole delayed-release capsules), Biaxin® (clarithromycin tablets), and Amoxil® (amoxicillin capsules).

There are no Pharmacology/Toxicology safety issues with the applicant's dosing regimen for the treatment of *H. pylori* infection and the application is approvable from a Pharmacology/Toxicology perspective.

See complete Pharmacology/Toxicology review by William Taylor, PhD entered into DARRTS on July 19, 2010.

4. Clinical Pharmacology/Biopharmaceutics

No clinical pharmacology data were included in the application. The applicant has referenced the findings of safety and efficacy for the Reference Listed Drugs Prilosec® (omeprazole delayed-release capsules), Biaxin® (clarithromycin tablets), and Amoxil® (amoxicillin capsules).

See complete Clinical Pharmacology review by Yori Harigaya, PhD entered into DARRTS on July 16, 2010.

5. Clinical Microbiology

No new data was reviewed. The application is approvable, with respect to Microbiology, pending an accepted version of the package insert. Several changes to the Microbiology Sections (12.1 and 12.4) of the proposed package insert were recommended, including addition of the mechanism of action for amoxicillin and clarithromycin and an updated reference for susceptibility testing method.

See complete Microbiology review by Anne Purfield, PhD entered into DARRTS on June 30, 2010.

6. Clinical/Statistical- Efficacy

No new clinical trial data was submitted. The applicant is relying on the findings of safety and effectiveness from the three approved products.

However, fixed-dose combination drug products are subject to 21 CFR 300.5, and the FDA generally applies the principles outlined in this regulation to co-packaged drug products. The "combination rule," as it is often referred to, states:

> "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

On November 17, 2009, the Statistical and Clinical Reviewers requested that the applicant address how each component of the co-packaged product (OCA) contributes to the effect of the co-packaged product by comparing 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). The Reviewers instructed that in each comparison the co-packaged product should be superior to the pair of drugs and the information can be supported by literature references.

In response to the Division's request, on January 6, 2010 the applicant 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.

The efficacy of the proposed omeprazole plus clarithromycin plus amoxicillin triple-therapy (OCA) was examined thorough a review of published clinical data, focusing on a comparison of the triple-therapy co-packaged product to each pair of drugs (i.e., OCA vs. clarithromycin plus amoxicillin (CA), OAC vs. omeprazole plus clarithromvcin (OC), OCA vs. omeprazole plus amoxicillin (OA)) in *Helicobacter pylori (H. pylori)* eradication in ulcer patients. A total of six randomized, comparative clinical trials were identified, out of which four evaluated

OCA versus CA, one compared OCA to OC, and the other one compared OCA to OA. In addition, a meta-analysis of 74 studies examined dual-therapy regimens with OC or OA versus OCA. 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 OCA regimen was more effective in eradicating *H. pylori* than CA, OC or OA. These studies were limited by the fact that none was conducted to support an NDA. Only 3 studies with OCA regimens were conducted in the US and had the same dosage regimen as the current application.

See complete Statistical review entered into DARRTS by Lan Zhang, PhD on July 16, 2010.

7. Safety

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

8. Advisory Committee Meeting

No Advisory Committee meeting was 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.

In the original submission the applicant submitted a request and justification (b) (4) of pediatric studies. Review of the applicant's justification was found inadequate and on October 26, 2009, the Division issued correspondence describing the justification needed to waive and/or defer pediatric studies, and a request to submit a revised Pediatric Plan by November 30, 2009.

The applicant submitted a revised Pediatric Plan on January 18, 2010, containing a second request and justification (b) (4) pediatric studies in patients (b) (4) . Again, the Division did not agree with the justification (b) (4) on May 11, 2010, issued correspondence requesting the submission by June 7, 2010 of a revised Pediatric Plan which would include a deferral of pediatric studies for the corresponding appropriate ages.

(b) (4)

To date, the applicant has not submitted a revised Pediatric Plan. Therefore, the application will be given a Complete Response action and the applicant will be requested to submit a pediatric drug development plan along with a request for deferral of pediatric studies for the treatment of *H. pylori* infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate *H. pylori*.

10. Other Relevant Regulatory Issues

On June 30, 2010 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).

11. Labeling

Proprietary Name
On October 4, 2010, the applicant submitted a request for review of the trade name (b) (4) DMEPA found that proposed trade name unacceptable, and communicated this information to the applicant during a teleconference date November 23, 2009. The reasons were as follows (as noted in the Label and Labeling review by Tara Turner entered into DARRTS on July 13, 2010):

- (b) (4)

- [redacted]

The applicant withdrew the trade name [redacted] in correspondence dated November 25, 2009.

On December 1, 2009, the applicant submitted a new trade name: [redacted] This name was reviewed by DMEPA and found unacceptable (see review by Tara Turner entered into DARRTS on March 2, 2010). DMEPA found this proposed name unacceptable [redacted] This information was also communicated to the applicant in correspondence dated March 2, 2010.

On April 20, 2010, the sponsor submitted a proposal for trade name [redacted] DMEPA reviewed this name and also found it unacceptable [redacted] (as noted in the Label and Labeling review by Tara Turner entered into DARRTS on July 13, 2010). This decision was communicated to the applicant during a teleconference on June 16, 2010 and the applicant withdrew the trade name on June 18, 2010.

No new proprietary name has been submitted to date.

Consults on PLR Package Insert

The Division consulted DDMAC on the package insert. The review was completed by Kathleen Klemm and entered into DARRTS on July 1, 2010. DDMAC's recommendations were accepted and incorporated into the revised PI by the Division.

The Division consulted the Maternal Health Staff (MHS) regarding the sections of the package insert which address use in pregnant women, labor and delivery, nursing mothers (Section 5 Warnings and Precautions and Section 8 Use in Specific Populations). The review was completed by Richardae Araojo and entered into DARRTS on June 2, 2010. MHS's recommendations were accepted and incorporated into the revised PI by the Division.

The Division consulted Iris Masucci, formerly of DDMAC/SEALD, via email on May 21, 2010 to review the package insert. The review was completed on June 7, 2010 and emailed back to the Division. The recommendations were accepted and incorporated into the revised PI by the Division.

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. For the purpose of comparison, DMEPA reviewed the labels and labeling for the currently marketed Prevpac® product obtained from the annual report dated (b) (4). Prevpac was selected as the comparator because its packaging configuration and dosage regimen are similar to that of the proposed product.

Although the Applicant closely followed the labels and labeling of Prevpac for the labeling of the proposed OCA product, DMEPA's evaluation noted areas where the presentation of information on the container labels, carton and insert labeling could be improved to minimize the potential for medication errors. See complete review by Tara Turner entered into DARRTS on July 13, 2010.

DMEPA's comments were sent to the applicant by the Division in a fax dated July 6, 2010. The applicant has not resubmitted the revised labels, to date.

12. Recommendations/Risk Benefit Assessment

The CDTL recommends a Complete Response action pending submission of a revised pediatric drug development plan and request for deferral of pediatric studies; and a package insert, carton and container labeling consistent with the revisions proposed by the Division.

The review team agrees with this intended action.

No REMS are required.

No Postmarketing Requirements or Commitments have been identified.

The following comments to the applicant will be conveyed in the Complete Response letter:

PEDIATRIC PLAN

Please, submit your pediatric drug development plan along with a request for deferral of pediatric studies for 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

1. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default htm.

   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.

2. Please submit draft carton and container labeling revised as described in our correspondence dated July 6, 2010.

3. Submit a copy of the labeling for the ANDA 62-881 (amoxicillin capsules) that you intend to use in the co-packaged product.

Appendix 1: FDA-Approved *Helicobacter pylori* Treatment Regimens

Antimicrobial Regimens	Dosage	Duration of Therapy	% Eradication Rates [95% Confidence Intervals] for Intent-to-Treat Analysis# (Per-protocol)
Bismuth subsalicylate Metronidazole Tetracycline (co-packaged as Helidac) H_2-blocker*	2 chewable tablets (525 mg) QID 250 mg QID 500 mg QID ulcer-treatment doses	14 days 14 days 14 days 28 days	72 [60, 84] NA x 2 studies (PP: 77%, 82%, 71%)
Clarithromycin (Biaxin) Omeprazole (Prilosec)	500 mg TID 40 mg QD, then 20 mg QD‡	14 days 14 days 14 days (beginning on Day 15)	NA x 2 studies (PP: 64%, 74%)
Clarithromycin (Biaxin) Amoxicillin Lansoprazole (Prevacid)	500 mg BID 1 gm BID 30 mg BID	10 days 10 days 10 days	81 [73.9, 87.6] (PP: 84%)
Clarithromycin (Biaxin) Amoxicillin Lansoprazole (Prevacid) Also co-packaged as PREVPAC®	500 mg BID 1 gm BID 30 mg BID	14 days 14 days 14 days	86 [73.3, 93.5] 83 [72.0, 90.8] 82 [73.9, 88.1] (PP: 86%, 92%)
Amoxicillin† Lansoprazole (Prevacid)	1 gm TID 30 mg TID	14 days 14 days	70 [56.8, 81.2] 61 [48.5, 72.9] (PP: 66%, 77%)
Clarithromycin (Biaxin) Amoxicillin Omeprazole (Prilosec)	500 mg BID 1 gm BID 20 mg BID, then 20 mg QD‡	10 days 10 days 10 days 18 days (beginning on Day 11)	69 [57, 79] 73 [61, 82] 83 [74, 91] (PP:78%, 84%, 90%)
Clarithromycin (Biaxin) Amoxicillin Esomeprazole (Nexium)	500 mg BID 1 gm BID 40 mg QD	10 days 10 days 10 days	77 [71, 82] 78 [67, 87] (PP: 84%, 85%)
Clarithromycin (Biaxin) Amoxicillin Rabeprazole (Aciphex)	500 mg BID 1 gm BID 20 mg BID	7 days 7 days 7 days	77 [71, 83] (PP: 84%^)
Bismuth subcitrate postassium, 140 mg Metronidazole, 125 mg Tetracycline hydrochloride, 125 mg (co-formulated at Pylera®) Omeprazole*	3 capsules of Pylera QID, after meals and at bedtime 20 mg BID after the morning and evening meal	10 days 10 days	MITT 87.7 [82.2, 93.2] (PP: 92.5%)

Key to Table

evaluable patients were defined as having confirmed active or history of (within 5 years) duodenal ulcer disease and *H. pylori* infection at baseline and for whom results were available for the 4-6 week post-treatment visit

∗ not included in co-package or co-formulation of the other components

▯ in patients with a history of duodenal ulcer disease

† for patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected

‡ in patients with an ulcer present at the time of initiation of therapy

^ evaluable patients were defined as having peptic ulcer disease (confirmed active or history of ulcer within 5 years) or symptomatic non-ulcer disease and *H. pylori* infection at baseline and for whom results were available at the 6 week post-treatment visit

APPEARS THIS WAY ON ORIGINAL

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

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

/s/

JOETTE M MEYER
07/19/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 50-824	**Applicant: DAVA Pharmaceuticals, Inc.**	**Stamp Date: June 19, 2009**
Drug Name: Patient Compliance Pack of Omeprazole Delayed Release, Clarithromycin Tablets and Amoxicillin Capsules(Triple Therapy Brand Name/TTBN)	**NDA/BLA Type: Standard Review; 505(b)(2)**	**Completion Date: August 3, 2009**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	**X**			Complete submission in paper; portions are electronic as well.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	**X**			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	**X**			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	**X**			
5.	Are all documents submitted in English or are English translations provided when necessary?	**X**			
6.	Is the clinical section legible so that substantive review can begin?	**X**			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	**X**			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	**X**			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			**X**	No clinical data are included in this NDA; instead the submission is based on reference to labeling for previously approved drugs
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			**X**	No clinical data are included in this NDA; instead the submission is based on reference to labeling for previously approved drug (omeprazole)
11.	Has the applicant submitted a benefit-risk analysis for the product?			**X**	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	**X**			505(b)(2). Reference drug is Omeprazole Delayed Release

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					Capsules
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			**X**	Labeling only; no clinical data
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			**X**	Labeling only; no clinical data
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			**X**	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			**X**	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			**X**	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			**X**	Labeling only; no clinical data
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			**X**	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			**X**	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			**X**	
22.	For drugs not chronically administered (intermittent or			**X**	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	short course), have the requisite number of patients been exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			**X**	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			**X**	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			**X**	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			**X**	Labeling only; no clinical data
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			**X**	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			**X**	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			**X**	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			**X**	Labeling only; no clinical data
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			**X**	Labeling only; no clinical data
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			**X**	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			**X**	
34.	Are all datasets to support the critical safety analyses available and complete?			**X**	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			**X**	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			**X**	Labeling only; no clinical data
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			**X**	
FINANCIAL DISCLOSURE					

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	Labeling only; no clinical data

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? **YES**

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

Not applicable.

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

1. It is noted that the applicant has several different versions of the proposed PLR package insert in the paper copy of the submission and the version that was provided electronically does not contain a Highlights section or a Table of Contents. The applicant should submit an electronic version in Word of the proposed package insert for the product which is complete and contains all required sections.

2. The applicant should provide the most recent versions of the approved labels for each of the three drugs in the proposed compliance pack (i.e. omeprazole, clarithromycin, and amoxicillin.)

3. The proposed label (b) (4) (b) (4)

4 (b) (4)

5. It is also suggested, but not required, that the applicant submit a proposed Trade Name for the Compliance Pack (TTBN).

Tafadzwa Vargas-Kasambira, M.D., M.P.H. August 3, 2009
Reviewing Medical Officer Date

Clinical Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50824	ORIG-1	DAVA PHARMACEUTICALS INC	AMOXICILLIN CAP 500MG/CLARITHROMYCIN TAB

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

/s/

TAFADZWA S VARGAS-KASAMBIRA
10/14/2009

JOETTE M MEYER
10/14/2009