CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050824Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 50-824	NDA Supplement #:	Efficacy Supplement Type SE-
Proprietary Name: None Established/Proper Name: Omeprazole/clarithromycin/amoxicillin Dosage Form: Co-package Strengths: Omeprazole 20 mg capsules/clarithromycin 500 tablets/amoxicillin 500 mg capsules		
Applicant: DAVA Pharmaceuticals		
Date of Receipt: September 22, 2009, CR letter July 20, 2010 Resubmission dated December 7 , 2010, Received December 8, 2010		
PDUFA Goal Date: February 8, 2011	Action Goal Date (if different): February 8, 2011	
Proposed Indication(s): Treatment of patients with H. Pylori infection and duodenal ulcer disease (active or up to 1-year history) to eradicate H. Pylori in adults.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Prilosec	Multiple sections of the package insert
Biaxin	Multiple sections of the package insert
Amoxil	Multiple sections of the package insert

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

This NDA provides for a co-packaged product of three approved products: Omeprazole (Prilosec), clarithromycin (Biaxin) and amoxicillin (Amoxil).
No clinical studies were conducted and all the labeling information is provided by the package inserts listed above.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒
*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐
*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Prilosec (omeprazole)	19-810	Yes
Biaxin (clarithromycin)	50-662	Yes
Amoxil (amoxicillin)	62-216/50-459	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒
*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐
*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Amoxil Capsules, 500 mg.

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a co-packaging of three approved products.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☒ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): Prilosec- 6,147,103
6,150,380
6,166,213
6,191,148
Amoxicillin-No patents listed
Clarithromycin-No patents Listed

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☒ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

Patent number(s): 6,147,103
6,150,380
6,166,213
(a) 6,191,148

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): AstraZeneca November 17, 2009
Merck November 17, 2009

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

Applicant submitted correspondence on January 19, 2010 certifying that the 45-day waiting period provided by Section 505(c)(3)(c) has expired without any action brought against DAVA for infringement of the subject patents.

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

/s/

JUDIT R MILSTEIN
02/08/2011
Concurred by 505(b)(2) staff on 1/18/11

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTRENTEROLOGY PRODUCTS

Consult for Labeling Review

NDA	50-824
Drug:	Omeprazole/Amoxicillin/Clarithromycin
Dose:	Omeprazole 20mg two times daily/ Amoxicillin 500mg two times daily/ Clarithromycin 500mg two times daily
Indication:	Treatment of *H. pylori* infection
Consulting:	Division of Special Pathogens and Transplant Products (DSPTP)
Reason for Consult:	Review proposed variation in content and format in Omeprazole portion of new combined label for consistency with approved label for Omeprazole
Date of Consult:	8/17/2010
Consultant:	Division of Gastroenterology Products
Medical Officer:	Lara Dimick, MD, FACS
Team Leader:	Hugo Gallo-Torres, MD, PhD
Division Deputy Director:	Andrew Mulberg, MD, FAAP, CPI
Project Manager:	Brian Strongin
Due Date:	10/20/2010
Completion Date:	10/18/2010

EXECUTIVE SUMMARY:
This review is in response to a consult from DSPTP that requested an evaluation of the proposed variations in content and format of the draft labeling that had occurred when the labeling for the three components of this combination product were combined. The consult requested review of the Proton Pump Inhibitor (PPI) component of two different combination products that are both designed to treat *Helicobacter Pylori* infections. This review will cover the label review of the omeprazole component of the omeprazole/clarithromycin/amoxicillin combination product (NDA 50824). (b) (4)

In general, the combined label covered all the information listed in the latest approved omeprazole label, and was adequately organized. However, these exceptions were noted:

- The adverse events associated with long term use (atrophic gastritis and bone fractures) were not listed in this labeling as the PPI is intended for one time use for ten days.
- The highlights section of the labeling did not mention all the drug interactions and use in special populations listed on the current omeprazole labeling. It was recommended that these be included, as detailed below.
- The combination product labeling did not mention co-administration with cilostazol, which is used for intermittent claudication. It is recommended that this information be included.
- (b) (4)

This review is organized such that the sections are titled and numbered to correspond with the titles and numbers on the labeling. The sections are listed only for those in which recommendations are made, the sections not listed were reviewed and no changes are suggested.

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

LARA DIMICK-SANTOS
02/07/2011

HUGO E GALLO TORRES
02/07/2011

ANDREW E MULBERG
02/07/2011

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	January 21, 2010
Application Type/Number:	NDA 050824
To:	Renata Albrecht, M.D., Director Division of Special Pathogen and Transplant Products
Through:	Melina Griffis, RPh, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Lubna Merchant, M.S., Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	(b) (4) (Omeprazole Delayed-release Capsules, USP, 20 mg, Amoxicillin Capsules, USP, 500 mg, and Clarithromycin Tablets, USP, 500 mg)
Applicant/sponsor:	DAVA Pharmaceuticals, Inc.
OSE RCM #:	2011-2

CONTENTS

1. INTRODUCTION

This review evaluates the labels and labeling submitted by the Applicant on December 7, 2010 for areas of vulnerability that could lead to medication errors. This submission responds to DMEPA's comments made in OSE review #2009-2034 on July 13, 2010.

2. METHODS AND MATERIALS REVIEWED

DMEPA reviewed the previous OSE review for (b) (4) dated July 13, 2010 (OSE #2009-2034) and evaluated the revised labels and labeling submitted by the Applicant on December 7, 2010 to see if the changes we requested in our previous review were addressed. In addition, we also reviewed the revised labels and labeling using Failure Mode and Effects Analysis (FMEA)[1]. See Appendices A through C for pictures of the labels and labeling.

3. CONCLUSIONS AND RECOMMENDATIONS

The Applicant has implemented our recommendations in the revised container labels and carton labeling. The majority of the revisions are satisfactory. However, we note that the statement " For one day of Therapy' is more prominent than the proprietary name as such and request that this statement be relocated and decreased in size. We provide recommendations in Section 3.2 and request they be communicated to the Applicant prior to approval. We also provide recommendations for the insert labeling in Section 3.1 Comments to the Division for discussion during the labeling meetings.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Karen Townsend at 301-796-5413.

3.1 COMMENTS TO THE DIVISION

The description of how the product is supplied is confusing. We request you revise sections 11: Description, section 3: Dosage Form and Strengths and section 16: How Supplied/Storage and Handling as follows. Replace the established names present at the beginning of this statement with the trade name as follows:

> "TTBN" are supplied in cartons containing ten individual daily administration cards. Each card contains:

3.2 COMMENTS TO THE APPLICANT

1. Patient Card Front

The statement "For one day of Therapy' is more prominent than the proprietary name. Thus we request you relocate the statement "For one day of Therapy" and the distributer information to appear below the established names and description. To accommodate this statement in this portion, you will need to relocate the statements "For further info....." and "Keep this and..." to appear below the tablets as shown below.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

---

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

/s/

LUBNA A MERCHANT
01/21/2011

MELINA N GRIFFIS
01/21/2011

CAROL A HOLQUIST
01/21/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 13, 2010
To:	Renata Albrecht, M.D., Director Division of Special Pathogen and Transplant Products
Through:	Zachary Oleszczuk, Pharm.D., Acting Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	(b) (4) (Omeprazole Delayed-release Capsules, USP, 20 mg, Amoxicillin Capsules, USP, 500 mg, and Clarithromycin Tablets, USP, 500 mg)
Application Type/Number:	NDA # 050824
Applicant:	DAVA Pharmaceuticals, Inc.
OSE RCM #:	2009-2034

***** This document contains proprietary and confidential information that should not be released to the public.*****

CONTENTS

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from the Division of Special Pathogen and Transplant Products (DSPTP) for evaluation of the labels and labeling of (b) (4) to identify areas that could contribute to medication errors. The Applicant submitted proposed container labels, carton and insert labeling for our review and comment.

1.2 REGULATORY HISTORY

On October 12, 2009, the Applicant submitted (b) (4) as the proposed proprietary name for this product. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed name unacceptable for the following reasons:

- (b) (4)

This information was communicated to the Applicant via teleconference on November 23, 2009 and the name was withdrawn on November 25, 2009. On December 2, 2009, the proposed proprietary name (b) (4) was submitted for review. DMEPA found this proposed name unacceptabl (b) (4) These findings were communicated to the Applicant in a letter dated March 2, 2010. On April 21, 2010, the proposed proprietary name (b) (4) was submitted. DMEPA found the name unacceptable (b) (4) These findings were communicated to the Applicant via teleconference on June 16, 2010 and the name was withdrawn on June 21, 2010.

2 METHODS AND MATERIALS

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database and reviewed proposed container labels, carton and insert labeling.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

Because Prevpac is a currently marketed product with the same indication of use and similar packaging configuration and dosing regimen as the proposed product, DMEPA searched the FDA Adverse Event Reporting System (AERS) database on April 12, 2010 to retrieve any medication errors involving risks that might relate to the proposed product. We searched AERS using the trade name term *"Prevpac"* and

the verbatim term *"Prev%"* with the MedDRA high level group term "Medication Errors" and preferred term "Product Quality Issue". We selected the option to include combination products.

We manually reviewed the reports to determine if medication errors occurred. If an error occurred, we reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis.

The search of the Adverse Event Reporting System identified six medication error reports involving Prevpac. Four of the reports described name confusion. One report described a drug interaction. The remaining report described adverse events and also indicated that the patient had not taken the drug on the prescribed schedule. However, no details regarding the noncompliance were provided. We did not identify any reports involving the labels, labeling, or packaging configuration of Prevpac. However, the lack of data does not indicate a lack of problems because medication errors are known to be underreported.

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used the principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling submitted April 21, 2010 (see Appendix A). The Applicant included a qualifying statement with the submission:

> *At this time, DAVA's draft labeling bears a mock product name, (b) (4) ", an abbreviation for "Triple Therapy Brand Name". Furthermore, mock graphics appear on the blister packs and serve only as place holders until such time that the proprietary name, official brand logo and graphics are established.*

In an e-mail dated April 27, 2010, we asked the Applicant if they conducted usability studies for the proposed packaging configuration. They responded that "…usability studies for the packaging configuration were not conducted, as the product packaging closely resembles PREVPAC, an already approved triple combination co-packaged product. Further, the packaging components used for the proposed NDA are usual and customary blister packaging components as approved in many other unit-dose packaging configurations that are already marketed in the USA." At that time we also requested working samples of the proposed packaging configuration. As of the date of this review we have not received samples for evaluation.

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

3 RECOMMENDATIONS

Although the Applicant closely followed the labels and labeling of the currently approved product, Prevpac, our evaluation noted areas where the presentation of information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations for the insert labeling in *Section 3.1 Comments to the Division* for discussion during the review team's label and labeling meetings. *Section 3.2 Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Karen Townsend, Project Manager, at 301-796-5413.

3.1 COMMENTS TO THE DIVISION

A. General Comments for All Labels and Labeling

1. The patient instructions presented on the container label provide recommendations for the dosing interval (e.g. 12 hours) along with other administration instructions (e.g. swallow whole, with liquid, before eating). However, this information is not presented in Section 2: Dosage and Administration of the package insert labeling. Present the dosage and administration instructions in a consistent manner across all product labels and labeling.
2. Ensure that the active ingredients are listed in a consistent order across all product labels and labeling. As currently presented, the insert labeling lists omeprazole/ amoxicillin/clarithromycin. However, the daily administration card lists the active ingredients in two ways: omeprazole/ amoxicillin/clarithromycin and omeprazole/clarithromycin/amoxicillin. The carton labeling lists omeprazole/clarithromycin/amoxicillin.

B. Insert Labeling

1. In the Highlights of Prescribing Information, list the established names and corresponding dosage forms of the individual components. As currently presented, only the established names of the individual components are listed (e.g. omeprazole, amoxicillin, clarithromycin) and the dosage form for the proposed product is listed as (b) (4) We defer to the Chemistry, Manufacturing, and Controls (CMC) review team for the proper presentation of the dosage form for the proposed product.
2. In Section 11: Description, the packaging information is confusing. Revise the statement (b) (4) as follows:

   "TTBN consists of a carton containing 10 individual daily administration cards. Each daily administration card contains:"
3. In Section 3: Dosage Form and Strengths and Section 16: How Supplied/Storage and Handling, the packaging information is confusing. Revise the statement (b) (4)

   "TTBN" is supplied as a carton containing 10 individual daily administration cards. Each daily administration card contains"

3.2 COMMENTS TO THE APPLICANT

A. General Comment for All Labels and Labeling

1. Please submit revised labels and labeling reflecting the approved proprietary name for this product along with all associated graphics and logo's, when available, for our review.
2. Ensure that the active ingredients are listed in a consistent order across all product labels and labeling. As currently presented, the insert labeling lists omeprazole/ amoxicillin/clarithromycin. However, the daily administration card lists the active ingredients in two ways: omeprazole/ amoxicillin/clarithromycin and omeprazole/clarithromycin/amoxicillin. The carton labeling lists omeprazole/clarithromycin/amoxicillin.

B. Container Labels: Patient Card Front (Trade and Sample)

1. [redacted] (b) (4)

2. Change the presentation of the active ingredients to include the strength immediately after the established name as follows:

   Omeprazole Delayed-release Capsules, USP, 20 mg

   Clarithromycin Tablets, USP, 500 mg

   Amoxicillin Capsules, USP, 500 mg

3. Use the numbers provided in the description of the active ingredients at the top of the dosage card (e.g. 1,2,3) to identify the actual corresponding capsules/tablets at the bottom of the card, as presented on the Prevpac labels.

4. Increase the prominence of the graphics representing the morning and evening doses to provide better differentiation, as presented on the Prevpac labels.

C. Container Labels: Blister Mat (Trade and Sample)

Relocate the "Rx Only" statement from the blister mat to the patient card front.

D. Carton Labeling: Trade

1. On the principal display, side, and back panels, directly below the proprietary name, add the dosage form and strength to the presentation of the active ingredients as follows:

   Omeprazole Delayed-release Capsules, USP, 20 mg

   Clarithromycin Tablets, USP, 500 mg

   Amoxicillin Capsules, USP, 500 mg

2. Change the presentation of the contents of the daily patient cards as follows, to improve clarity:

   Each daily patient card contains:

   2 lavender and grey delayed-release capsules, each containing 20 mg of omeprazole

   2 white, biconvex beveled edge capsule shaped coated tablets, each containing 500 mg of clarithromycin

   4 peach and orange capsules each containing amoxicillin trihydrate equivalent to 500 mg of amoxicillin

E. Carton Labeling: Sample

1. On the principal display panel, directly below the proprietary name, add the dosage form and strength to the presentation of the active ingredients as follows:

   Omeprazole Delayed-release Capsules, USP, 20 mg

   Clarithromycin Tablets, USP, 500 mg

   Amoxicillin Capsules, USP, 500 mg

2. Change the presentation of the contents of the card as follows, to improve clarity:

   Contains one day of therapy:

2 lavender and grey delayed-release capsules, each containing 20 mg of omeprazole

2 white, biconvex beveled edge capsule shaped coated tablets, each containing 500 mg of clarithromycin

4 peach and orange capsules each containing amoxicillin trihydrate equivalent to 500 mg of amoxicillin

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

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

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

/s/

TARA P TURNER
07/13/2010

ZACHARY A OLESZCZUK
07/13/2010

DENISE P TOYER
07/13/2010

CAROL A HOLQUIST
07/13/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: July 1, 2010

To: Judit Milstein, Chief Project Management Staff
Division of Special Pathogen and Transplant Products (DSPTP)

From: Kathleen Klemm, Regulatory Review Officer,
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader, DDMAC
Michael Sauers, Acting DTC Group Leader, DDMAC
Sharon Watson, Regulatory Review Officer, DDMAC
Wayne Amchin, Regulatory Health Project Manager, DDMAC

Subject: NDA 050824

DDMAC labeling comments for omeprazole/clarithromycin/amoxicillin

---

In response to DSPTP's January 15, 2010, consult request, DDMAC has reviewed the draft product labeling (PI) for omeprazole/clarithromycin/amoxicillin. DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled, "Dava labeling to OSE-DDMAC clean 28June10.doc" that was sent via email from DSPTP to DDMAC on June 28, 2010.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on this proposed material.

If you have any questions regarding the PI, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

29 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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

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

/s/

KATHLEEN KLEMM
07/01/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team Label Review

Date: May 27, 2010 **Date Consulted:** April 23, 2010

From: Richardae Araojo, PharmD
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: The Division of Special Pathogen and Transplant Products (DSPTP)

Drug: TTBN (omeprazole, amoxicillin, clarithromycin) patient compliance pack; NDA (b) (4)

Subject: Labeling Review

Materials Reviewed: Pregnancy and Nursing Mothers subsections of TTBN labeling.

Consult Question: Please review the sponsor's proposed language and recommend alternative language if necessary.

INTRODUCTION

On June 18, 2009, DAVA Pharmaceuticals, Inc. submitted a 505(b)(2) application (NDA (b) (4) for TTBN, a patient compliance pack consisting of omeprazole delayed release capsules, clarithromycin tablets, and amoxicillin capsules. The proposed indication for this application is for the treatment of *H. pylori* infection and duodenal ulcer disease (active or up to one year history) to eradicate *H. pylori* in adults. The Division of Special Pathogen and Transplant Products (DSPTP) consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mother's subsections of the sponsor's proposed labeling.

BACKGROUND

TTBN is a daily administration pack containing two Omeprazole delayed-release 20mg capsules, four amoxicillin 500mg capsules, and two clarithromycin 500mg tablets for oral administration. Omeprazole is a gastric acid (proton) pump inhibitor and is labeled as pregnancy category C based on adverse findings in animal developmental studies and a lack of adequate and well controlled studies in pregnant women. However, omeprazole pregnancy labeling includes human data on omeprazole use during pregnancy and the associated pregnancy outcomes. Clarithromycin is macrolide antibiotic and is labeled as pregnancy category C based on adverse developmental findings in multiple animal species (monkey, rat, mice and rabbits) and a lack of adequate and well controlled studies in pregnant women. Amoxicillin is an antibiotic and is labeled as pregnancy category B based on animal studies that did not show adverse reproductive or developmental findings and a lack of adequate and well controlled studies in pregnant women.

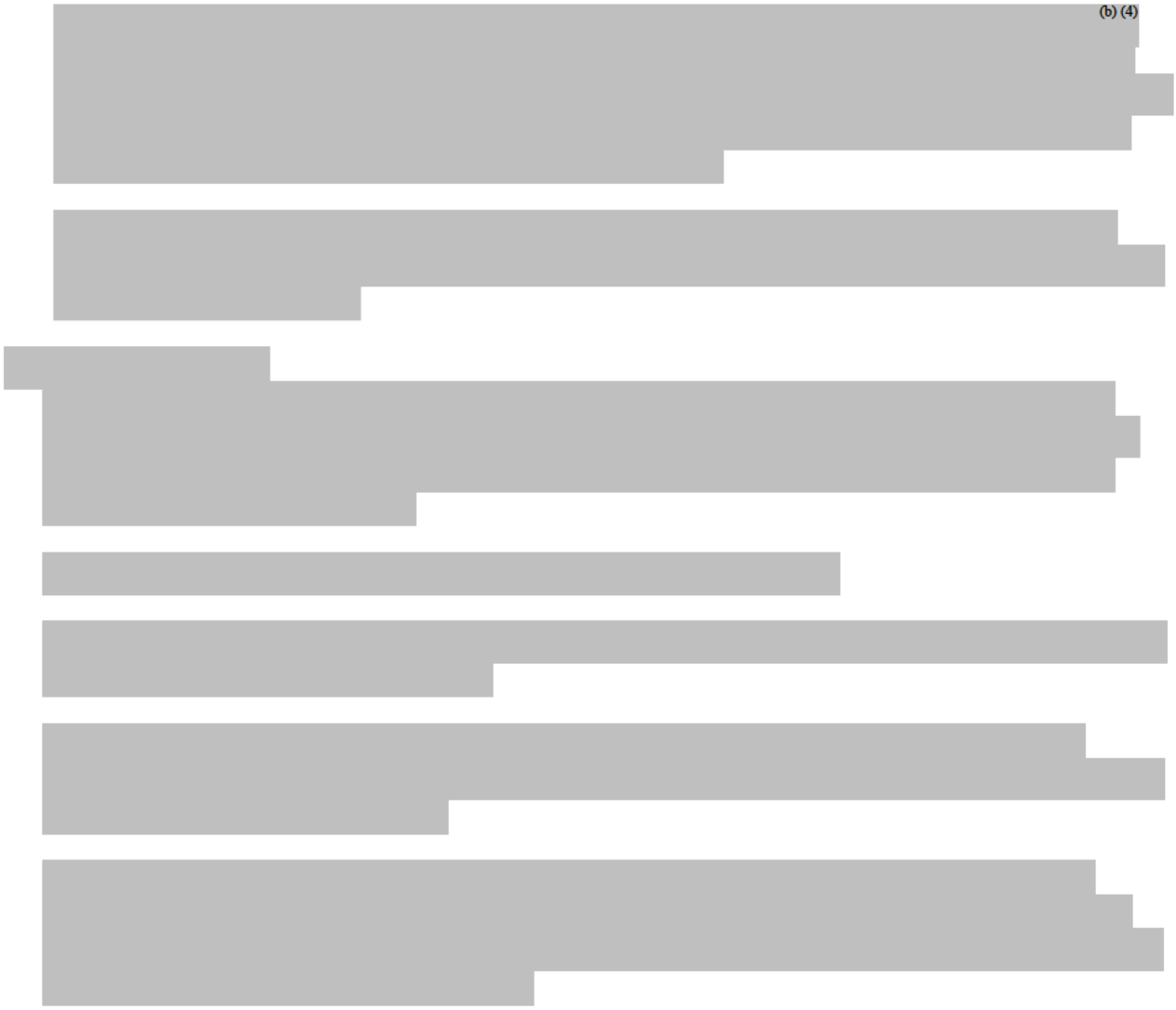
The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). When appropriate, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. This review provides suggested revisions to the sponsor's proposed Pregnancy and Nursing Mother's subsections of TTBN labeling.

SUMBMITTED MATERIAL

Sponsor's Proposed Labeling Related to Pregnancy and Nursing Mothers

(b) (4)

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



DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is being written and cleared, the MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

For this review, the MHT revised sections of TTBN labeling related to pregnancy and lactation. The sponsor's proposed labeling includes data on the use of omeprazole in pregnant and lactating women. However, the labeling does not include human data on the use of amoxicillin or clarithromycin during pregnancy or lactation.

Published data are available on the use of amoxicillin and clarithromycin in pregnant and lactating women. In data from a clinical trial and population-based studies, maternal use of amoxicillin did not increase the risk for congenital malformations in more than 2000 women who

used amoxicillin during pregnancy. Published pharmacokinetic data suggest lower plasma concentrations of amoxicillin in pregnant women compared to nonpregnant women; however, it is not known if these pharmacokinetic differences correlate with clinical differences in infection cure rates.[1] In addition, published data on more than 90 pregnancy exposures to clarithromycin did not show an increased risk of major malformations.[2,3,4]

Based on a summary of published data provided by the National Library of Medicine's Drugs and Lactation Database, amoxicillin and clarithromycin are excreted in human milk in small amounts and are not expected to cause adverse effects in human-milk fed infants.[5] In addition, the American Academy of Pediatrics classified amoxicillin as *usually compatible* with breastfeeding, but does not provide an evaluation for clarithromycin.[6]

Based on the availability of human pregnancy and lactation data for amoxicillin and clarithromycin, the MHT recommends inclusion of relevant data in TTBN labeling.

RECOMMENDATIONS

1. The MHT recommends that the division issue a labeling supplement request letter to the sponsor requesting inclusion in labeling of relevant human data on clarithromycin and amoxicillin exposure during pregnancy and lactation.

2. Provided below is a track changes version of the MHT's recommended revisions to the sponsor's proposed labeling.

[1] REPROTOX evaluation for Amoxicillin. Accessed through MICROMEDEX. REPROTOX is a scientifically reviewed source that evaluates and summarizes published literature on human and animal pregnancy exposures.
[2] Wogelius P, Gislum M, Norgaard M, et al. Maternal use of erythromycin and risk of congenital malformations: a population-based cohort study. Pharmacoepidemiol Drug Saf 2006;15(Suppl1):S85.
[3] Tellum R, Shechtman S, Arnon J, et al. Pregnancy outcome after gestational exposure to the new macrolides: a prospective controlled cohort study. Reprod Toxicol 2005; 20(3): 484-5.
[4] Bar-Oz B, Diav-Citrin O, Shechtman S, et al. Pregnancy outcome after gestational exposure to the new macrolides" A prospective multi-center observational study. Eur J Obstet Gynecol Reprod Biol 2008;141:31-34.
[5] The National Library of Medicine's Drugs and Lactation Database search for amoxicillin and clarithromycin. http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT
[6] Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics. 108:776-89, 2001.

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

---

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

/s/

RICHARDAE T ARAOJO
05/28/2010

Karen B FEIBUS
05/28/2010
I agree with the recommendations contained in this review.

LISA L MATHIS
06/02/2010

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 50-824	NDA Supplement #:	Efficacy Supplement Type:
Proprietary Name: TTBN (Omeprazole 20 mg delayed-release capsules, amoxicillin 500 mg capsules and clarithromycin 500 mg delayed-release capsules)		
Applicant: DAVA Pharmaceuticals, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: June 18, 2009 Date of Receipt: June 19, 2009 Date clock started after UN: n/a		
PDUFA Goal Date: April 19, 2010	Action Goal Date (if different): April 5, 2010	
Filing Date: August 18, 2009	Date of Filing Meeting: July 27, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed Indication(s): 1. Treatment and eradication of H. Pylori infection & 2. Treatment of duodenal ulcer diseases (active or up to 1-year history) in adults.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: n/a ***(Refer to Appendix A for further information.)***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***		☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ YES ☒ NO Resubmission after refuse to file? ☐ YES ☒ NO		
Part 3 Combination Product? ☐ YES ☒ NO		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ YES ☒ NO Fast Track ☐ YES ☒ NO Rolling Review ☐ YES ☒ NO Orphan Designation ☐ YES ☒ NO Rx-to-OTC switch, Full ☐ YES ☒ NO Rx-to-OTC switch, Partial ☐ YES ☒ NO Direct-to-OTC Other: ☐ YES ☐ NO		☐ YES ☒ NO PMC response ☐ YES ☒ NO PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify
Collaborative Review Division (*if OTC product*): n/a		
List referenced IND Number(s): P-IND 101,174		

PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☐ YES n/a ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	
Does another product have orphan exclusivity for the same indication? Comments: **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***	☐ YES ☒ NO ☐ YES ☐ NO

Comments:	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**: This product is a co-packaging of 3 approved ANDA products that have no unexpired exclusivity.	☐ YES # years requested: ☒ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	☐ **Not applicable** ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☒ NO
4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** ***Comments:***	☐ YES ☒ NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content

Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☐ All electronic ☒ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	All submissions are in both electronic and paper
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO ***Submitted Forms(F)**:* ☒ YES F *356h (see page 5)* ☒ NO *patent information F 3542a* ☒ NO *financial disclosure F 3454/ 3455 (no clinical study)* ☒ NO *user fee cover sheet F 3542a* Sponsor's User fee form: 3397 ☒ NO *clinical trials F 3674* ***Certifications**:* ☒ YES *debarment certification,* ☒ YES *patent certification(s),* ☒ YES *field copy certification,* ☒ NO *pediatric certification.*
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ NO; CTD only This is mixed electronic/paper submission in CTD only for the electronic information

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	N/A ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☐ YES ☒ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it*	☒ YES ☐ NO

did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…" **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☒ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**: This NDA is a 505 (b)(2) submission and no clinical trials were conducted.	☐ YES ☒ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**: The sponsor did not request a waiver or deferral of pediatric studies. They will be asked to include this information in their resubmission of the NDA.	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☐ NO
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the***	☐ YES ☒ NO

Pediatric Exclusivity Board is needed). **Comments**:	
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (Physician PI) ☒ Patient Package Insert (PPI, included in the Patient Card (Front and Blister Mat) on both commercial package & professional sample) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels (commercial package & professional sample) ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**: The sponsor withdrew this application due to deficiencies related to MMA (Medicare Modernization Act) on 8-20-2009. A consult will be sent to DDMAC upon resubmission.	☐ YES ☒ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☒ Not Applicable NO
REMS consulted to OSE/DRISK? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	☐ Not Applicable ☐ YES

Comments: This application was withdrawn on 8-20-2009, two days after the filing date. A consult will be send upon resubmission of the NDA.	☒ NO
OTC Labeling	**n/a**
Check all types of labeling submitted. **Comments**:	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: Advice letter issued March 18, 2008, under PIND 101174 contains responses and comments regarding the submission of this NDA.	☐ YES Date(s): ☒ NO
Any Special Protocol Assessment (SPA) agreements?	☐ YES

If yes, distribute letter and/or relevant minutes before filing meeting. **Comments**:	Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 7/27/2009

NDA #: 50-824

PROPRIETARY/ESTABLISHED NAMES: TTBN (Omeprazole 20 mg delayed-release capsules, amoxicillin 500 mg capsules and clarithromycin 500 mg capsules)

APPLICANT: DAVA Pharmaceuticals, Inc.

BACKGROUND: This NDA provides for the co-packaging of 3 approved ANDA products (amoxicillin, clarithromycin, omeprazole). The basis for this submission is the FDA approved labeling for omeprazole delayed-release capsules which specifies the use of triple therapy 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.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christina H. Chi, Ph.D.	Y
	CPMS/TL:	Judit Milstein	Y
Cross-Discipline Team Leader (CDTL)	**Joette M. Meyer, Pharm.D.**		Y
Clinical	Reviewer:	Tafadzwa S. Vargas-Kasambira, M.D., M.P.H.	Y
	TL:	Joette M. Meyer, Pharm.D.	Y
Social Scientist Review (*for OTC products*)	Reviewer:	n/a	
	TL:		
Labeling Review (*for OTC products*)	Reviewer:	n/a	
	TL:		
OSE	Reviewer:		
	TL:	Melissa Truffa	N

Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Ann Purfield, Ph.D.	Y
	TL:	Shukal Bala, Ph.D.	Y
Clinical Pharmacology	Reviewer:	Yoriko Harigaya, Ph.D.	Y
	TL:	Phil Colangelo, Ph.D.	Y
Biostatistics	Reviewer:	HongLing Zhou, Ph.D.	Y
	TL:	Karen Higgins, Sc.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Stephen Hundley, Ph.D.	Y
	TL:	William Taylor, Ph.D.	Y
Statistics, carcinogenicity	Reviewer:	n/a	
	TL:		
Product Quality (CMC)	Reviewer:	Jeff Medwid	Y
	TL:	Rapti Madurawe, Ph.D.	Y
Facility (*for BLAs/BLA supplements*)	Reviewer:	n/a	
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:	n/a	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	n/a	
	TL:		
Other reviewers	DDMAC (Labeling):		

OTHER ATTENDEES: Renata Albrecht, M.D. Division Director, DSPTP
David Roeder ADRA, OAP

505(b)(2) filing issues? **If yes,** list issues: **Comments:** There were no filing issues. However, since this is a 505(b)(2) submission relying on 3 ANDA approved products, the Division requested a telecon with the sponsor, DAVA, to clarify the following issues	☐ Not Applicable ☐ YES ☒ NO

1. The submission does not identify all three reference listed drugs (RLD) that form the basis for the safety and effectiveness of the proposed product, except for Prilosec. There is no RLD identified for neither the clarithromycin nor the amoxicillin components of this proposed co-packaged product. 2. The sponsor also submitted a "paragraph I" patent certification for Prilosec, This is unacceptable because of the multiple unexpired patents listed in the Orange Book for NDA 19-810 for Prilosec. Because of MMA (Medicare Modernization Act) regulations, the sponsor cannot amend the submission with information related to RLDs and respective patent certifications. Therefore, they will need to withdraw the application and resubmit with the correct information. For detailed information on the discussion, refer to the minutes of the meeting issued on September 15, 2009.	
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**: There are no clinical studies.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No Clinical studies (safety and efficacy) were conducted. Therefore, no Clinical study sites inspection is needed.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: • ***the application is to enhance patient compliance*** • ***did not raise significant safety or efficacy issues*** • ***the application did not raise***

or efficacy issues ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	***significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease***
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested?	☐ Not Applicable ☒ YES ☐ NO

If no, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☐ YES ☒ NO; IR letter to be sent requesting status of sites for inspection ☐ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☒ NO ☐ YES ☐ NO
FACILITY (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Christina Chi/Judit Milstein

GRMP Timeline Milestones:
8/18/09: filing date

Comments: This application was withdrawn on 8/20/2009, hence, no GRMP Timeline Milestones is applicable, and **no 74 day letter was issued.**

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional):

	☒ Standard Review ☐ Priority Review **Comments:** The sponsor withdrew the application on August 20, 2009, two days after the application was filed. Therefore, no 74 day letter was issued.
	ACTIONS ITEMS
☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74-Applicant withdrew the application; no 74 day letter was issued.
☐	Other

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

/s/

CHRISTINA H CHI
09/15/2009

JUDIT R MILSTEIN
09/16/2009
CSO Filing Review