

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
050824Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

| | |
|---------------------------|---|
| NDA: 50-824 | Submission Date(s): December 7, 2010 |
| Brand Name | TBD |
| Generic Name | Omeprazole /Clarithromycin/Amoxicillin |
| Reviewer | Yoriko Harigaya, Pharm.D. |
| Team Leader | Philip M. Colangelo, Pharm.D., Ph.D. |
| OCP Division | DCP IV |
| OND Division | DSPTP |
| Sponsor | DAVA Pharmaceuticals Inc. |
| Submission Type; Code | 505(b)(2) |
| Formulation; Strength(s) | Co-packaged product containing the following 3 drug formulations: Omeprazole Delayed-Release Capsules 20 mg Clarithromycin Tablets 500 mg Amoxicillin Capsules 500 mg |
| Proposed Indications | 1. Treatment and eradication of <i>H. Pylori</i> infection 2. Treatment of duodenal ulcer disease (active or up to 1-year history) in adults |
| Dosage and Administration | Omeprazole delayed-release capsule 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily, for 10 days, in the morning and evening before eating a meal |

DAVA Pharmaceuticals Inc. has submitted NDA 50-814 on September 21, 2009 as a 505(b)(2) submission for a co-packaged product of omeprazole delayed-release capsules 20 mg, clarithromycin 500 mg tablets, and amoxicillin 1000 mg capsules for the treatment and eradication of *H. Pylori* infection and the treatment of duodenal ulcer disease (active or up to 1-year history) in adults. On December 7, 2010, the applicant submitted the response to our Complete Response letter issued on July 20, 2010. The amended labeling submitted on February 7, 2011 was reviewed and is acceptable from a Clinical Pharmacology perspective.

Yoriko Harigaya, Pharm.D.
Reviewer
Clinical Pharmacology
DCP4/OCP/OTS

Concurrence

Kellie Reynolds, Pharm.D.
Deputy Director
Clinical Pharmacology
DCP4/OCP/OTS

Concurrence

Philip Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology
DCP4/OCP/OTS

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

/s/

YORIKO HARIGAYA
02/08/2011

KELLIE S REYNOLDS
02/08/2011
Signing for Phil Colangelo

CLINICAL PHARMACOLOGY REVIEW

| | |
|---------------------------|---|
| NDA: 50-824 | Submission Date(s): June 19, 2009 |
| Brand Name | TBD |
| Generic Name | Omeprazole /Clarithromycin/Amoxicillin |
| Reviewer | Yoriko Harigaya, Pharm.D. |
| Team Leader | Philip M. Colangelo, Pharm.D., Ph.D. |
| OCP Division | DCP IV |
| OND Division | DSPTP |
| Sponsor | DAVA Pharmaceuticals Inc. |
| Submission Type; Code | 505(b)(2) |
| Formulation; Strength(s) | Co-packaged product containing the following 3 drug formulations: Omeprazole Delayed-Release Capsules 20 mg Clarithromycin Tablets 500 mg Amoxicillin Capsules 500 mg |
| Proposed Indications | 1. Treatment and eradication of <i>H. Pylori</i> infection 2. Treatment of duodenal ulcer disease (active or up to 1-year history) in adults |
| Dosage and Administration | Omeprazole delayed-release capsule 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily, for 10 days, in the morning and evening before eating a meal |

DAVA Pharmaceuticals Inc. has submitted NDA 50-814 as a 505(b)(2) submission for a co-packaged product of omeprazole delayed-release capsules 20 mg, clarithromycin 500 mg tablets, and amoxicillin 1000 mg capsules for the treatment and eradication of *H. Pylori* infection and the treatment of duodenal ulcer disease (active or up to 1-year history) in adults. The proposed dosing regimen is omeprazole delayed-release capsule 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily, for 10 days, in the morning and evening before eating a meal.

ANDA 075-576 omeprazole delayed-release capsule, ANDA 065-178 clarithromycin tablet and ANDA 062-881 amoxicillin capsule were previously approved for the treatment and eradication of *H. Pylori* infection and the treatment of duodenal ulcer diseases (active or up to 1-year history) in adults by the FDA. Currently, the sponsor submitted this NDA in support of the use of a co-packaged product in the 10-day treatment for the same indication. There was no new Clinical Pharmacology information provided, and therefore, no Clinical Pharmacology review is needed.

Attachment 1 contains Clinical Pharmacology revisions to the most current version of the proposed labeling.

Yoriko Harigaya, Pharm.D.
Reviewer
Clinical Pharmacology
DCP4/OCP/OTS

Concurrence

Philip Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology
DCP4/OCP/OTS

Attachment 1

**Omeprazole Delayed-Release Capsules / Clarithromycin Tablets / Amoxicillin Capsules Label
with Clinical Pharmacology Review**

Version: July 16, 2010

30 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 PHARMACEUTICA LS 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/

YORIKO HARIGAYA
07/16/2010

PHILIP M COLANGELO
07/16/2010

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

| | Information | | Information |
|----------------------------------|-------------------------------------|-------------------------|--|
| NDA/BLA Number | 50-824 | Brand Name | N/A |
| OCP Division (I, II, III, IV, V) | IV | Generic Name | Omeprazole /Clarithromycin/Amoxicillin |
| Medical Division | DSPTP | Drug Class | PPI/Macrolide/Penicillin |
| OCP Reviewer | Yoriko Harigaya, Pharm.D. | Indication(s) | Treatment of <i>H. pylori</i> infection and duodenal ulcer disease |
| OCP Team Leader | Philip M. Colangelo, Pharm.D., Ph.D | Dosage Form | Capsule (Delayed-Release)/ Capsule/ Tablet |
| Pharmacometrics Reviewer | N/A | Dosing Regimen | BID for 10 days |
| Date of Submission | June 18, 2009 | Route of Administration | Oral |
| Estimated Due Date of OCP Review | July 15, 2009 | Sponsor | DAVA Pharmaceuticals Inc. |
| Medical Division Due Date | N/A | Priority Classification | Standard |
| PDUFA Due Date | N/A | | |

Clin. Pharm. and Biopharm. Information

| | “X” if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|------------------------------|-----------------------------------|----------------------------------|--------------------------|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | | | | |
| Tabular Listing of All Human Studies | | | | |
| HPK Summary | | | | |
| Labeling | | | | |
| Reference Bioanalytical and Analytical Methods | | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|---|--|--|---|--|
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD - | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD - | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies | | | | |
| Bio-waiver request based on BCS | | | | |
| BCS class | | | | |
| Dissolution study to evaluate alcohol induced dose-dumping | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | | 0 | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|------------|-----------|------------|----------------|
| Criteria for Refusal to File (RTF) | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | √ | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | √ | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | | √ | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | √ | | | |
| 5 | Has a rationale for dose selection been submitted? | √ | | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | √ | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | √ | | | |
| 8 | Is the electronic submission searchable, does it have appropriate | √ | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | | |
|---|--|---|--|---|--|
| | hyperlinks and do the hyperlinks work? | | | | |
| Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) | | | | | |
| Data | | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | | | √ | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | √ | |
| Studies and Analyses | | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | √ | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | √ | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | | √ | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | | √ | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | √ | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | √ | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | √ | | | |
| General | | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | √ | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | √ | |

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

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

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

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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

/s/

YORIKO HARIGAYA
08/18/2009

PHILIP M COLANGELO
08/18/2009