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APPLICATION NUMBER:

050824Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number: 50-824
Supporting Document: Not Applicable
Applicant's letter date: February 7, 2011
CDER stamp date: February 7, 2011
Product: (b) (4) (Omeprazole 20 mg delayed-released capsules, amoxicillin 500 mg capsules and clarithromycin 500 mg capsules)
Applicant: DAVA Pharmaceuticals, Inc.
Review Division: Division of Special Pathogen and Transplant Products
Reviewer: William Taylor, PhD, DABT
Division Director: Renata Albrecht, MD
Project Manager: Judit Milstein

The current submission dated February 7, 2011 contains a revised package insert for a co-packaged product of OMEPRAZOLE DELAYED-RELEASE CAPSULES, CLARITHROMYCIN TABLETS, and AMOXICILLIN CAPSULES from DAVA Pharmaceuticals, Inc.

Stephen G. Hundley, PhD, DABT evaluated Sections 8.1 (Pregnancy) and 13 (Nonclinical Toxicology) of the package insert in a review in DARRTS, which was finalized on July 19, 2010. The applicant's current proposed language for these sections of the package insert are substantially the same as recommended in Dr. Hundley's 2010 review. From a Pharmacology/Toxicology perspective, I recommend approval of the application.

William H. Taylor, PhD, DABT
Pharmacology/Toxicology Supervisor

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/s/

WILLIAM H Taylor
02/07/2011

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PHARMACOLOGY TOXICOLOGY NDA REVIEW AND EVALUATION

Application Number: 50-824
Supporting Document: Not Applicable
Applicant's letter date: 9/21/09
CDER stamp date: 9/22/09
Product: (b) (4) (Omeprazole 20 mg delayed-released capsules, amoxicillin 500 mg capsules and clarithromycin 500 mg capsules)
Applicant: DAVA Pharmaceuticals, Inc.
Review Division: Special Pathogen and Transplant Products
Reviewer: Stephen Hundley, Ph.D., DABT
Supervisor/Team Leader: William Taylor, Ph.D., DABT
Division Director: Renata Albrecht, MD
Project Manager: Judit Milstein

NDA REVIEW MEMO

NDA 50-824 (505(b)(2) Application)

Proposed Indication: *Helicobacter pylori* Eradication for the Reduction of Risk of Duodenal Ulcer Recurrence

EXECUTIVE SUMMARY

The applicant (DAVA Pharmaceuticals) submitted NDA 50-824 as a 505(b)(2) application and relied for proof of safety and efficacy upon the Reference Listed Drugs (RLDs) for Prilosec® (omeprazole), Biaxin® (clarithromycin), and Amoxil® (amoxicillin). The applicants' proposed marketing name is (b) (4) (Omeprazole Delayed-Release Capsules, Clarithromycin Tablets and Amoxicillin Capsules).

The indication proposed by the applicant is (b) (4) *a copackaged product containing a proton pump inhibitor, a macrolide antimicrobial, and a penicillin class antibacterial, is indicated for the treatment of patients with Helicobacter pylori infection and duodenal ulcer disease (active for up to one year history) to eradicate H. pylori."*

The dosage and administration is identical to the currently approved Physician Labeling Rule (PLR) for Prilosec® treatment of *H. pylori* as indicated below:

Adult regimen: Omeprazole 20 mg plus clarithromycin 500 mg plus amoxicillin 1,000 mg, each given twice daily for 10 days in the morning and evening before eating a meal. In patients with an ulcer present at initiation of therapy, an additional 18 days of omeprazole once daily is recommended.

The prepackaged pack of daily administration cards is to contain:

- *Two omeprazole delayed-release capsules USP, 20 mg*
- *Two clarithromycin tablets USP, 500 mg*
- *Four amoxicillin capsules USP, 500 mg*

There are no Pharmacology/Toxicology safety issues with the applicant's dosing regimen for the treatment of *H. pylori* infection and NDA 50-824 can be approved.

Labeling Language

The recommended Pharmacology/Toxicology language for the pertinent areas of the PLR is listed below:

8.1 Pregnancy

Pregnancy Category C (based on animal studies of omeprazole and clarithromycin)

There are no adequate and well controlled studies of omeprazole, clarithromycin or amoxicillin (used separately or together) in pregnant women. Clarithromycin demonstrated adverse developmental effects in four animal species at clinically relevant doses. Omeprazole increased embryo-fetal loss in rabbits, but animal studies and multiple human studies do not show an increased risk for major malformations. TTBN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and there is no appropriate alternative therapy [*see Warnings and Precautions (5.1)*].

Omeprazole:

Multiple cohort studies in pregnant women exposed to omeprazole during the first trimester do not show an increased risk of congenital malformations. The majority of experience with omeprazole use during human pregnancy includes first trimester exposure and the duration of use is rarely specified. Three epidemiological studies compared the frequency of congenital malformations among infants born to women who used omeprazole during pregnancy with the frequency of malformations among infants of women exposed to H₂-receptor antagonists or controls. One population-based prospective cohort study from the Swedish Medical Birth Registry, reported 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. *In utero* exposure to omeprazole was not associated with an increased risk of malformations (odds ratio 0.82, 95% CI 0.50–1.34), low birth weight or low Apgar score. While the number of stillbirths and infants born with ventricular septal defects were slightly higher in the omeprazole-exposed group, these findings may have been due to chance and do not establish a causal relationship to omeprazole exposure.

A retrospective cohort study reported on 689 pregnant women exposed to either H₂-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6–5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5–8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with non-exposed women was 0.9 (95% CI 0.3–2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to non-teratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1–5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ among the groups. The sample size in this study had 80% power to detect a 5-fold increase in the rate of major malformations.

Reproductive and developmental toxicology studies conducted in rats and rabbits during organogenesis at oral omeprazole doses up to 28 times the human dose of 40 mg/day did not show any evidence of fetal structural abnormalities. However, dose-related increases in embryo-lethality, fetal resorptions, and pregnancy loss occurred when pregnant rabbits received omeprazole at doses about 2.8 to 28 times the human dose of 40 mg/day. In a peri- and post-natal development study, when pregnant rats received omeprazole at doses about 2.8

to 28 times the human dose of 40 mg/day, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring [See [Nonclinical Toxicology \(13.3\)](#)].

Clarithromycin:

When pregnant monkeys received 70 mg/kg/day oral clarithromycin (approximately equivalent to the MRHD on a mg/m² basis) fetal growth retardation occurred at plasma levels that were 2 times the human serum levels achieved at the maximum recommended human dose (MRHD).

A low incidence of cardiovascular anomalies were observed in fetuses in two rat embryo-fetal studies of clarithromycin administered orally to dams on gestation days 6 to 15 at doses of 150 mg/kg/day, which resulted in plasma levels approximately 2 times the human serum levels achieved at the MRHD.

Four embryo-fetal studies in mice revealed a variable incidence of cleft palate following oral doses of 500 mg/kg/day and 1000 mg/kg/day (2 and 4 times the MRHD on a mg/m² basis, respectively) during organogenesis (gestation days 6 to 15). The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels achieved at the MRHD.

No teratogenic effects occurred in offspring from two studies in pregnant rabbits that received oral clarithromycin doses up to 125 mg/kg/day (approximately 2 times the maximum recommended human dose on a mg/m² basis) or intravenous doses of 30 mg/kg/day during the period of major organogenesis.

Amoxicillin:

Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Omeprazole

In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times a human dose of 20 mg/day, as expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both males and females; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 6 times a human dose of 20 mg/day, based on body surface area) for one year, and then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret.

In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a small number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.2 to 6.5 times the human dose on a body surface area basis). No astrocytomas were observed in female rats in this study or in a males or females from a 2-year carcinogenicity study in Sprague-Dawley rats at the high dose of 140.8 mg/kg/day (about 57 times the human dose on a body surface area basis). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vivo* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in the *in vitro* Ames test, an *in vitro* mouse lymphoma cell forward mutation assay, and an *in vivo* rat liver DNA damage assay.

Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on fertility and reproductive performance.

William Taylor, Ph.D., DABT
Pharmacology/Toxicology Team Leader
Division of Special Pathogen and Transplant Products

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

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/s/

WILLIAM H Taylor
07/19/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 50-824 Applicant: DAVA Pharmaceutical Stamp Date: 6/18/09

Drug Name: TTBN NDA/BLA Type: 505(b)(2)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not Applicable
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not Applicable
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not Applicable
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		505(b)(2) application; paper submission for nonclinical information
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Not applicable
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION
FILEABLE? YES**

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

No pharmacology/toxicology issue with the 505(b)(2) application with approved use of omeprazole, amoxicillin, and clarithromycin (20/500/500 mg) in a blister pack.

Stephen Hundley, Ph.D., DABT

Aug., 18, 2009

Reviewing Pharmacologist

Date

William Taylor, Ph.D., DABT

Team Leader/Supervisor

Date

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/s/

STEPHEN G HUNDLEY
08/18/2009

WILLIAM H Taylor
08/18/2009