

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208253Orig1s000

PHARMACOLOGY REVIEW(S)

Memo to the Division File (Labeling Review - Addendum)

NDA 208253, Submitted 6/26/2015

Doxycycline Hyclate Capsules 75 mg

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Reviewer, DAIP

Through: Wendelyn Schmidt, Pharmacology/Toxicology Supervisor, DAIP

Date: Jan. 1, 2016

Background:

The Applicant, Aqua Pharmaceuticals, submitted a 505(b)(2) NDA requesting marketing approval to license doxycycline hyclate capsules at 75 mg. No new pharmacology/toxicology data was submitted to this NDA. This NDA was submitted before 6/30/2015 and therefore is not subject to PLLR labeling requirements. The Applicant originally proposed no changes to the pharmacology/toxicology relevant sections of the labeling, remaining identical to previously approved labels for other doxycycline hyclate products with identical dosage forms, dosage strengths, and indications. In a discussion with Dr. Barbara Hill, the pharm/tox team leader in Division of Dermatology and Dental Products, it was learned that the product labeling for Oracea® (doxycycline hyclate), a low dose (40 mg) tablet of doxycycline indicated for treatment of inflammatory lesions of rosacea (and not for treatment (b) (4) of infections), contains nonclinical genetic toxicology and carcinogenicity data from animal studies that does not appear in the anti-infective product labeling. An information request was sent to the Applicant on 12/21/2015 containing the following comment:

“Please review the package insert for Oracea® (doxycycline) capsules, particularly subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. This subsection contains nonclinical data from 2-year carcinogenicity studies in both mice and rats administered doxycycline by oral gavage, as well as male fertility and reproductive performance information in rats administered oral doxycycline. Determine if this nonclinical information is relevant to your drug product and proposed indications. At a minimum, the statements describing the absence of long term carcinogenicity studies with doxycycline and the unknown effects on male fertility in animals will need to be corrected. Please revise and submit the updated package insert to the Division for review as soon as possible.”

In response to our information request, the Applicant submitted the revised labeling containing changes to Subsection 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility for their drug product on 1/08/2016 (Module 1.14.1.3 Draft Labeling). The Applicant proposed no changes to Section 8 or Subsection 13.2 of the labeling. The Applicant's proposed changes to Subsection 13.1 can be found in italics and italics/strikethrough below. The reviewer's recommended changes are in bold and bold/strikethrough below:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of ACTICLATE® (doxycycline hyclate (b)(4)) and TRADENAME (doxycycline hyclate (b)(4)) (b)(4) have not been conducted.

However, a 2 year **carcinogenicity study** (b)(4) **with doxycycline administered daily by oral gavage to adult rats (20, 75, 200 mg/kg/day)** (b)(4) **demonstrated an increase in uterine polyps in female rats at 200 mg/kg/day (10 times the maximum recommended daily adult dose of ACTICLATE® and TRADENAME based on body surface area comparison) with no change in tumor incidence in male rats at the same dose. A 2-year carcinogenicity study with doxycycline administered daily by oral gavage to adult (b)(4) male (b)(4) (maximum dose 150 mg/kg/day) and female (b)(4) (maximum dose 300 mg/kg/day) showed no changes in tumor incidence, at approximately 4 and 7 times the maximum recommended daily adult dose of ACTICLATE® and TRADENAME, based on a body surface area comparison, respectively.**

*Mutagenesis and fertility studies have not been conducted with ACTICLATE® and TRADENAME. Mutagenesis studies (b)(4) with doxycycline demonstrated no potential to cause genetic toxicity in an *in vitro* point mutation study with mammalian cells or in an *in vivo* micronucleus assay in CD-1 mice. However, data from an *in vitro* mammalian chromosomal aberration assay conducted in CHO cells (b)(4) suggest that doxycycline is a weak clastogen. Oral administration of doxycycline to Sprague-Dawley rats showed adverse effects on fertility and reproduction including increased time for mating, reduced sperm motility, velocity and concentration as well as increased pre and post implantation loss. Reduced sperm velocity was seen at the lowest dosage tested, 50 mg/kg/day, which is 2.5 times the maximum recommended daily adult dose (b)(4) of ACTICLATE® and TRADENAME (b)(4). Although doxycycline impairs the fertility of*

rats when administered at sufficient dosages, the effect of ACTICLATE® and TRADENAME on human fertility is unknown.

(b) (4)



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

/s/

TERRY J MILLER
01/15/2016

WENDELYN J SCHMIDT
01/15/2016

Memo to the Division File

NDA 208253, Submitted 6/26/2015

Doxycycline Hyclate Capsules 75 mg

From: Terry J. Miller, Ph.D., Pharmacology/Toxicology Reviewer, DAIP

Through: Wendelyn Schmidt, Pharmacology/Toxicology Supervisor, DAIP

Date: October 29, 2015

Background:

The Applicant, Aqua Pharmaceuticals, submitted a 505(b)(2) NDA requesting marketing approval to license doxycycline hyclate capsules at 75 mg. No new pharmacology/toxicology data was submitted to this NDA. The labeling for the relevant pharmacology/toxicology sections are identical to previously approved labels. This NDA was submitted before 6/30/2015 and therefore is not subject to PLLR labeling requirements. The impurities and degradants detected in the final drug product are within specified limits described in the USP monograph for doxycycline hyclate. The excipients (microcrystalline cellulose NF and magnesium stearate NF) in the proposed formulation are in other approved products, are compendial, and their safety is well established. The ^{(b) (4)} hard gelatin capsule is used in other FDA approved products.

Recommendation:

There are no pharmacology/toxicology issues with the approval of this NDA.

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

/s/

TERRY J MILLER
11/04/2015

WENDELYN J SCHMIDT
11/04/2015