# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 50-805

# MICROBIOLOGY REVIEW

# DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS (DAIOP)
# CLINICAL MICROBIOLOGY REVIEW
# CONSULTATION FOR HFD 540

NDA 50-805 Date Review Completed: May 15, 2006

Date Company Submitted: 29 July 2005
Dare Received (HFD520): 3 August 2005
Date Assigned: 10 August 2005
Date Completed: 13 January 2006
Reviewer: Connie R. Mahon, MS & Avery Goodwin, Ph.D.

## NAME AND ADDRESS OF APPLICANT:

Collagenex Pharmaceuticals, Inc.
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## CONTACT PERSON:

Christopher Powala
Vice President, Drug Development & Regulatory Affairs

## DRUG PRODUCT NAME:

Established Name: Doxycycline ——— capsules
Proposed Name for drug product: Oracea™
Product Code: COL-101
Chemical Name: alpha-6-deoxy-5-oxytetracycline
Chemical formula: $C_{22}H_{24}N_2O_8 \cdot H2O$
Molecular Weight: 462.46

## PROPOSED INDICATION:

To ——— inflammatory lesions in patients with rosacea

## PROPOSED DOSAGE FORM, DOSAGE, STRENGTH, ROUTE OF ADMINISTRATION:

40 mg oral ——————— capsule taken once daily.

## DURATION OF TREATMENT:

Duration of treatment: 16 weeks

## TYPE OF SUBMISSION:

**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS (DAIOP)**
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Microbiology Review Consult for HFD 540

**RELATED SUBMISSION:**

IND 67,833 S/021

**PURPOSE OF SUBMISSION:**

The Applicant, Collagenex Pharmaceuticals, Inc. submits an original new drug application (NDA 50-805) for Oracea™ for oral administration to — inflammatory lesions in patients with rosacea. Oracea™ is doxycycline —, which is synthetically derived from oxytetracycline. The dosage form is 40 mg — capsule. Oracea™ is to be taken once daily in the morning.

The Division of Dermatologic and Dental Drug Products has requested a review and assessment of the proposed clinical microbiology subsection of the package insert.

**SUMMARY AND RECOMMENDATIONS**

Collagenex Pharmaceutical has submitted a new drug application (NDA 50-805) for Oracea™ for oral administration to — inflammatory lesions in patients with rosacea. Oracea™ is doxycycline — which is synthetically derived from oxytetracycline. The dosage form is 40 mg — capsule.

From the clinical microbiology perspective, this NDA submission may be approved provided that the Applicant makes the appropriate changes to the microbiology section of the proposed label recommended by the Agency.

The Microbiology Reviewer provides the following changes regarding the Microbiology section of the label for Oracea™:

**AGENCY PROPOSED MICROBIOLOGY SECTION OF THE LABEL**

**MICROBIOLOGY**

*Doxycycline is a member of the tetracycline class of antibacterial drugs. The plasma concentrations of doxycycline achieved with this product during administration (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION) is less than the concentration required to treat bacterial diseases. In vivo microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina.*

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*TRADENAME **should not** be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.*

Under precautions it is suggested that the following be added:

*Bacterial resistance to the tetracyclines may develop in patients using TRADE NAME;*

*Because of the potential for tetracycline-resistant bacteria to develop during the use of TRADE NAME, it should be used only as indicated.*

**BACKGROUND INFORMATION**

Collagenex Pharmaceutical submits a new drug application that references NDA 50-744 for Periostat (doxycycline hyclate) 20 mg capsules and NDA 50-783 for Periostat 20 mg tablets to demonstrate that doxycycline hyclate does not induce recognizable effect on the composition of the gingival flora or result in an increase in antibiotic resistance.

The Applicant proposes the name Oracea for the drug product (doxycycline capsules). Doxycycline is synthetically derived from oxytetracycline. The proposed indication is to inflammatory lesions in patients with rosacea.

Doxycycline is the International non-proprietary name (INN), US Adopted Name (USAN), and the British Approved Name (BAN) for the drug substance used in Oracea™ doxycycline 40 mg capsule. The capsule consists of instantaneous-release (IR) beads containing a total of 30 mg doxycycline and controlled release (CR) beads containing a total of 10 mg. The beads are filled into a hard gelatin capsule shell. (Section 2.7.2.4.1 page 194 NDA 50-805).

With regard to clinical microbiology, the Applicant intends to use cross-study reports from previously submitted NDAs. The Applicant submits two microbiology studies that have assessed the effects of doxycycline hyclate 20 mg BID dose regimen on microflora of the skin for review.

The Sponsor plans to cross-reference previous studies that evaluated Periostat (doxycycline hyclate) 20 mg BID and demonstrated that a 9-18 month regimen of Periostat did not exert a discernable effect on the composition of the subgingival flora or result in an increase in antibiotic resistance. The three microbiology studies to be cited by reference to NDA 50-744 include:

- Study 5732.11A: A 3 month, randomized, placebo-controlled clinical study to

evaluate the microbial effects of five dose regimens of doxycycline hyclate on the oral cavity

- Study 5732.11 E&F: A 12 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects of 10 mg QD, 20 mg QD, and 20 mg BID of doxycycline hyclate on the oral cavity
- Study 5732.11 H: A 9 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects 20 mg BID of doxycycline hyclate on the oral cavity

For the COL- 101 NDA, the Sponsor plans to submit two microbiology studies for review:

- Study 5732.11 J: A 9 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects 20 mg BID of doxycycline hyclate on the intestinal and vaginal flora
- Study DERM-301: A 6 month, randomized, double-blind, placebo-controlled study to determine the microbial effects 20 mg bid of doxycycline hyclate on the skin microflora

In the draft product labeling, the Sponsor proposes the following in the microbiology subsection and asks if the Agency agrees.

*"Microbiology: Doxycycline is a member of the tetracycline class of antibiotics. The plasma concentration of doxycycline achieved with this product during administration is*

[ ]

The Sponsor also proposes to include the following statements regarding the mechanism of action:

[ ]

## INTRODUCTION

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