CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-805

PHARMACOLOGY REVIEW

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**50-805**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**8/3/05**
PRODUCT:	**Oracea**
INTENDED CLINICAL POPULATION:	**Patients with Inflammatory Lesions from Rosacea**
SPONSOR:	**CollaGenex Pharmaceuticals**
DOCUMENTS REVIEWED:	**Vols. 1, 2 and 4**
REVIEW DIVISION:	**Division of Dermatology and Dental Drug Products (HFD-540)**
PHARM/TOX REVIEWER:	**Carmen Booker, Ph.D.**
PHARM/TOX SUPERVISOR:	**Paul Brown, Ph.D.**
DIVISION DIRECTOR:	**Stanka Kukich, M.D.**
PROJECT MANAGER:	**Shalini Jain**

Date of review submission to Division File System (DFS): May 1, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: The product is approvable with respect to nonclinical concerns.

B. Recommendation for nonclinical studies: The sponsor has committed to conduct a necessary second carcinogenicity study in mice during Phase 4.

C. Recommendations on labeling: None.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Doxycycline did not elicit signs of toxicity when administered to Crl:CD(SD)BR rats by gavage on a single occasion at a dose of 500 mg/kg. Of two males and two females that received single doses of 750 mg/kg, only one death occurred (a male). In a 13-week study in which doxycycline was administered to rats at dosages of 25, 100, 400 and 600 mg/kg/day, toxicity was observed at 400 mg/kg/day and above, including adverse clinical signs, a trend toward reduced weight gain, suppressed erythrocytic parameters, reduced plasma protein, reduced weight and hematopoietic activity of the spleen, and mild inflammation of the GI tract, including moderate to marked focal erosions of the stomach. The NOAEL was determined to be 100 mg/kg/day. Daily administration of doxycycline to cynomolgus monkeys at doses of 5, 15 or 30 mg/kg/day for 12 months was generally well tolerated and produced minimal signs of toxicity.

Doxycycline demonstrated no potential to cause genetic toxicity in an *in vitro* point mutation study with mammalian cells (CHO/HGPRT forward mutation assay) or in an *in vivo* micronucleus assay conducted in CD-1 mice. Data from an *in vitro* assay with CHO cells for potential to cause chromosomal aberrations suggest that doxycycline is a weak clastogen.

A two-year bioassay was conducted in rats to assess the carcinogenicity of doxycycline. The only remarkable, statistically significant, treatment-related observation in the study was an increased incidence of uterine polyps in females in the high-dose group (200 mg/kg/day). The sponsor has committed to conduct a second carcinogenicity study in mice during Phase 4.

Doxycycline, as a tetracycline, is likely to induce tooth staining in children when administered to children or pregnant women. Doxycycline adversely affected fertility and reproductive performance of rats. Doxycycline is in pregnancy category D.

B. Pharmacologic activity

Doxycycline is an antibiotic compound as well as an inhibitor of collagenase. However, the speculative mechanism of action in treatment of rosacea is via the inhibition of neutrophil activity and several neutrophil-associated pro-inflammatory processes. No adverse pharmacological activity has been observed in the cardiovascular, respiratory and central nervous systems following doxycycline treatment.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues relevant to the clinical use of Oracea™.

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