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™.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

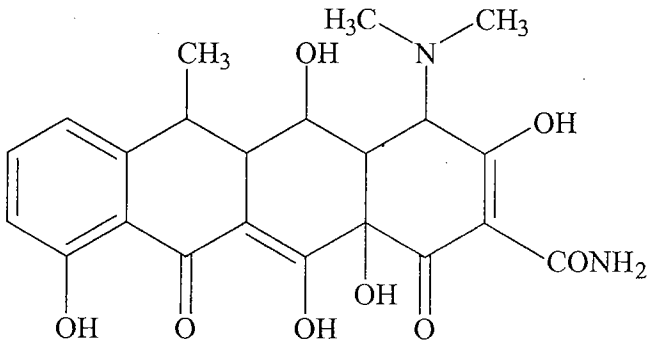
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 50-805
Review number: 1
Sequence number/date/type of submission: N-000/3-Aug-2004
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: CollaGenex Pharmaceuticals

Reviewer name: Carmen D. Booker, Ph.D.
Division name: Division of Dermatology and Dental Drug Products
HFD #: 540
Review completion date:

Drug:

Trade name: Oracea
Generic name: Doxycycline monohydrate
Code name: COL-101
Chemical name: 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate
CAS registry number: 17086-28-1
Molecular formula/molecular weight: $C_{22}H_{24}N_2O_8 \cdot H_2O$ / 462.46
Structure:



Relevant INDs/NDAs/DMFs: IND 67,833; ; NDA 50-744; NDA 50-783; IND ;

Drug class: Antibiotic/collagenase inhibitor

Intended clinical population: To inflammatory lesions in patients with rosacea

Clinical formulation: Quantitative Composition (mg/capsule)

Doxycycline Monohydrate, USP/NF
Hypromellose, —— USP/NF
Methacrylic Acid Copolymer, —— USP/NF
Triethyl Citrate, USP/NF
Talc, USP/NF

Sugar Spheres, —— USP/NF
Hard Gelatin Capsule — Beige Opaque

[ ]

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: None. Please see the Pharmacology review of NDA 50-744 for evaluation of applicable data. NDA 50-744 is held by the same sponsor (CollaGenex) as the current NDA and contains the applicable study reports.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

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.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: The speculative mechanism of action is via anti-inflammation. Neutrophil-mediated processes contribute, in part, to the development of inflammatory lesions in patients with rosacea. Doxycycline has been shown to inhibit neutrophils activity and several neutrophil-associated pro-inflammatory processes.

Drug activity related to proposed indication: The inhibition of pro-inflammatory processes, such as those associated with nitric oxide production or interleukin-6, caused by doxycycline decreases the inflammatory response associated with rosacea.

2.6.2.3 Secondary pharmacodynamics

Doxycycline is an antibiotic compound with activity against many species of bacteria when administered at sufficient doses. Tetracyclines, such as doxycycline, are primarily bacteriostatic and have antimicrobial activity against a wide range of gram-positive and gram-negative organisms. It is believed that tetracyclines exert their antimicrobial effect via the inhibition of protein synthesis.

2.6.2.4 Safety pharmacology

The literature and previous clinical experience with Periostat® and Vibramycin suggest that there are no safety pharmacology concerns associated with doxycycline.

2.6.2.5 Pharmacodynamic drug interactions

The labeling for Oracea™ will include the same information on precautions regarding drug interactions as the approved product labeling for Periostat®.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No new pharmacology or safety pharmacology studies have been conducted on doxycycline. See summaries above.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

No new nonclinical pharmacokinetic studies on doxycycline have been conducted. The pharmacokinetics of doxycycline has been discussed extensively in scientific literature. Doxycycline is well-absorbed from the GI tract. Protein binding is extremely variable. Published values for the serum half-life and renal clearance of doxycycline are 14.5-22 hours and 16 mL/minute, respectively. Doxycycline is excreted in the urine and feces as unchanged drug.

2.6.4.2 Methods of Analysis

Methods of analysis are discussed within individual study reviews. Please see reviews associated with NDA 50-744.

2.6.4.3 Absorption

Doxycycline is well absorbed after oral administration.

2.6.4.4 Distribution

As stated in the approved labeling for Periostat®, doxycycline is greater than 90% bound to plasma proteins.

2.6.4.5 Metabolism

Major metabolites of doxycycline have not been identified.

2.6.4.6 Excretion

Doxycycline is excreted in the urine and feces as unchanged drug.

2.6.4.7 Pharmacokinetic drug interactions

Enzyme inducers such as barbiturates, carbamazepine and phenytoin decrease the half-life of doxycycline. Bismuth subsalicylate, proton pump inhibitors, antacids and nutritional supplements containing aluminum, calcium, magnesium or iron impair the absorption of doxycycline.

2.6.4.8 Other Pharmacokinetic Studies

No new nonclinical pharmacokinetic studies on doxycycline have been conducted.

2.6.4.9 Discussion and Conclusions

No new nonclinical pharmacokinetic studies on doxycycline have been conducted.

2.6.4.10 Tables and figures to include comparative TK summary

No new nonclinical pharmacokinetic studies on doxycycline have been conducted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No new nonclinical pharmacokinetic studies on doxycycline have been conducted. See summaries above.

2.6.6 TOXICOLOGY

Note: All nonclinical studies were conducted using doxycycline hyclate (Periostat®). In humans, Oracea™, 40 mg QD has been shown to be equivalent (using least squares mean C_{max} and AUC_{ss} values) to the approved product Periostat® tablets, 20 mg BID (according to the sponsor).

2.6.6.1 Overall toxicology summary

General toxicology: Please see the reviews associated with NDA 50-744. Briefly, 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.

Genetic toxicology: Please see the reviews associated with NDA 50-744. Briefly, 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.

Carcinogenicity: 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.

Reproductive toxicology: 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.

2.6.6.2 Single-dose toxicity

Please see the reviews associated with NDA 50-744. No new toxicity studies on doxycycline have been submitted.

2.6.6.3 Repeat-dose toxicity

Please see the reviews associated with NDA 50-744. No new toxicity studies on doxycycline have been submitted.

2.6.6.4 Genetic toxicology

Please see the reviews associated with NDA 50-744. No new genetic toxicology studies on doxycycline have been submitted.

2.6.6.5 Carcinogenicity

Please see the reviews associated with NDA 50-744. No new carcinogenicity studies on doxycycline have been submitted.

The sponsor has submitted a protocol for a carcinogenicity study in mice to be conducted as a Phase 4 commitment. The sponsor intends to conduct a 7-day dose range finding study in July 2006. A subsequent 4-week toxicology study will be conducted in September 2006. The sponsor anticipates that a 13-week toxicology study will begin in January 2007. During June 2007, the sponsor will file the proposed doses for use in the 104-week carcinogenicity study with the Agency for review by the CAC. The 104-week carcinogenicity study will begin in August of 2007. The sponsor anticipates having a final report for the carcinogenicity study available in February 2010.

2.6.6.6 Reproductive and developmental toxicology

Please see the reviews associated with NDA 50-744. No new reproductive and developmental toxicology studies on doxycycline have been submitted.

2.6.6.7 Local tolerance

Oracea™ is orally ingested; therefore, local tolerance is not a safety concern.

2.6.6.8 Special toxicology studies

Please see the reviews associated with NDA 50-744. No new special toxicology studies on doxycycline have been submitted.

2.6.6.9 Discussion and Conclusions

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.

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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.

2.6.6.10 Tables and Figures

Please see the reviews associated with NDA 50-744. No new toxicity studies on doxycycline have been submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

No new toxicology studies on doxycycline have been submitted. See summaries above.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

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

Unresolved toxicology issues: Sponsor has committed to conduct a 2-year carcinogenicity study with doxycycline monohydrate in mice.

Recommendations: NDA 50-805 is approvable in regard to pharmacologic and toxicologic concerns.

Suggested labeling: The labeling for Oracea™ with regard to nonclinical safety will be the same as that approved for Periostat®, with the exception of the section entitled "Carcinogenesis, Mutagenesis, Impairment of Fertility". In this section, the sponsor was asked (in an information request sent April 7, 2006) to use AUC values for exposure comparisons. In a response sent to the Agency on April 19, 2006, the sponsor adjusted the label using AUC data collected in preclinical studies (see attached table). The label is acceptable to this reviewer.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Table 2. Comparison of Preclinical Versus Human Exposure

Study	Dose (mg/kg/day)	Dose (mg/m^2/day)	AUC_{0-24} (ng*h/ml), average	Dose increase (factor)	AUC increase (factor)
13 week oral tox. in rats	0 (Control)	0 (Control)	-		
	25 mg/kg	162.5 mg/m^2	13,711		
	100 mg/kg	650 mg/m^2	54,642	4	4
	400 mg/kg	2600 mg/m^2	166,490	4	3.05
	600 mg/kg	3900 mg/m^2	152,062	1.5	0.91
2 year carcinogenicity in rats	20 mg/kg	130 mg/m^2	10,968[a]		
	75 mg/kg	487.5 mg/m^2	40,981[a]		
	200 mg/kg	1300 mg/m^2	91,925[b]		
Reproductive toxicology, rat	50 mg/kg	325 mg/m^2	27,321[a]		
Human Exposure	0.5 mg/kg	22.2 mg/m^2	7.543*		
Carcinogenicity 200 mg/kg multiple vs. human dose	400	58.6	12.2		
Reproductive 50 mg/kg multiple vs. human dose	100	5.6	3.6		

[a] interpolation calculated assuming dose-linearity
[b] interpolation calculated as $Y = 372.83x + 17359$
* data from study COL-101-SSPK-106

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/s/

Carmen Booker
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