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APPLICATION NUMBER:

50-805

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA Number	50-805
Letter Date(s)	July 29th, 2005, February 10 th , 2006 and April 7 th , 2006
Brand Name	Oracea TM
Generic Name	Doxycycline _____ .0 mg _____
Reviewer	Abimbola Adebawale Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DCP3
OND Division	OND-540
Applicant	Collagenex Pharmaceuticals, PA
Related IND(s)	67,833 and _____
Submission Type; Code	Original NDA
Formulation	Capsules
Indication	Tc _____ : inflammatory lesions in patients with rosacea

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1 Executive Summary

The applicant has submitted a 505 (b) (1) application for OraceaTM (doxycycline _____ 40 mg capsules. It is intended to be taken once daily in the morning to _____ inflammatory lesions in patients with rosacea. Oracea capsules consists of immediate release (IR) beads (75 %) and delayed-release (DR) beads (25 %) containing 30 mg and 10 mg of doxycycline, monohydrate, respectively. The applicant stated that the DR beads are formed by coating the IR

beads with a _____ The IR and DR beads are then filled into a hard gelatin capsule shell.

Although doxycycline is classified as an antimicrobial agent, the applicant stated that at the systemic concentrations provided by Oracea™ 40 mg, doxycycline is not effective as an antimicrobial agent and appears to exert its beneficial actions on inflammatory lesions of rosacea by mechanisms independent of antimicrobial activity. In light of this, the goal of their formulation development was to achieve bioequivalence to Periostat® (doxycycline hyclate tablets) 20 mg in terms of area under the concentration time curve (AUC) while keeping the maximum plasma level (Cmax) below 1.0 µg/mL so as not to exceed the threshold for antimicrobial activity in vitro, which may increase the risk of developing resistant microorganisms. Periostat® (NDA 50-783) is an approved drug product that was previously developed by the applicant, for use twice daily, as an adjunct to scaling and root planning to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

1.1 Recommendation (s):

The clinical pharmacology and biopharmaceutics data submitted for Oracea™ capsules adequately characterized its pharmacokinetics following single and multiple dose administration. The data also demonstrated that the rate and extent of doxycycline from Oracea™ was equivalent to that of Periostat®, the immediate release drug product, at steady state, but not following a single dose. The rate and extent of absorption of doxycycline obtained following a single dose of Oracea capsules was higher than that obtained following administration of Periostat® tablets BID. Since Oracea™ is intended for chronic dosing in patients with rosacea, this may not be a safety concern in actual use since the systemic exposure following multiple dosing was found to be equivalent. In addition the applicant included safety data obtained from their Phase 3 trials for Oracea in this application. This data is currently being reviewed by the medical reviewer.

Therefore, from a clinical pharmacology and biopharmaceutics perspective the applicant has met the requirement outlined in 21 CFR 320 and, their application is acceptable provided that the applicant agrees to tighten the dissolution specifications as proposed below. We also recommend that the applicant incorporate our labeling changes as outlined in Section 3 of this review in their final label.

Comment to be conveyed to the Applicant:

The dissolution specifications are not acceptable because the proposed specifications at the 2-hr time point are too wide to ensure batch to batch quality. Based on the dissolution data generated with the clinical/bioavailability batches, it is recommended that the 2 hr specification be revised from _____ dissolved to _____ and _____ % dissolved.

1.2 Phase IV Commitments: None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics (CPB) Findings:

The pharmacokinetics of doxycycline following administration of single or multiple doses of Oracea 40 mg have been evaluated in four studies. All four pharmacokinetic studies

were conducted in healthy adult volunteers of both genders and used an open-label, randomized, crossover study design. Two initial studies (PERIO-DOXYSR-103 and 104) and two subsequent studies (COL-101-SDPK-105 and COL-101-SSPK-106) were conducted. These studies will be labeled as 103, 104, 105 and 106 for the most part of this review. All of these studies used the same formulation of the drug product as that proposed for marketing. A dissolution method and specifications were also proposed.

The *in vivo* PK studies primarily evaluated the following:

- The pharmacokinetics after single and multiple dosing of Oracea in healthy subjects
- The effect of food on Oracea after a single dose
- The relative bioavailability of Oracea[®] capsules (40 mg) once daily to Periostat 20 mg immediate release (IR) tablets BID after single and multiple dosing in healthy subjects
- The effect of gender on the pharmacokinetics of doxycycline

In addition to these four PK studies, a pilot clinical study performed during the development of Oracea that showed doxycycline is absorbed mainly in the upper part of the gastrointestinal tract and, a published study by Grahnén et al (1994) that showed that the bioavailability of doxycycline monohydrate is reduced after pre-treatment with omeprazole were summarized in the NDA.

Please note that the following names have been used interchangeably during the development of Oracea and were used in this application in various source documents: "Oracea," "Doxycycline"

Single Dose Pharmacokinetics

Absorption:

The pharmacokinetics of doxycycline following single dose administration of Oracea was evaluated in three pharmacokinetic studies (#'s 103, 104 and 105). The rate (C_{max}) and extent (AUC 0-24 or AUC 0-72) of absorption of doxycycline obtained in all three studies were comparable. The median T_{max} of doxycycline ranged from about 1 hour to 4 hours in all three studies.

In contrast, the rate and extent of absorption of doxycycline from Oracea was not similar to that of Periostat BID following single dose administration. In studies 103 and 104, the applicant compared the relative bioavailability of doxycycline after a single dose of Oracea to currently marketed Periostat 20 mg administered BID (12 hours apart) in healthy volunteers. The results of both studies indicated that Oracea had a higher rate and extent of absorption. This was further demonstrated by the 90 % CI for C_{max} (125 to 172 % for Study # 103 and 147 to 203 % for study # 104) and AUC 0-24 (97.7 to 128 % for study # 103 and 114 to 144 % for study # 104) being outside the 80 to 125 % range.

Excretion:

Following a single dose of Oracea 40 mg capsules the mean (SD) half life of doxycycline in healthy volunteers (aged ~18-45 years old) was 15.1 (5.49), and 21.2 (7.64) hrs respectively (Study # 103 and 105).

Food Effect

The applicant evaluated the effect of food on the pharmacokinetics of a single dose of Oracea (40 mg) capsules in study # 105, a randomized, two-way crossover study in 30 male and female subjects. The concomitant administration of Oracea with a high-fat meal resulted in a decrease in the rate and extent of absorption (C_{max} and AUC) by about 45 % and 22 %, respectively, compared to dosing under fasting conditions. There was a delay of about 1 hour for the mean T_{max} in the fed state compared to the fasted state. In addition the T_{max} was much more variable (range of _____ nrs) in the fed state compared to the fasted state (range of _____ hrs). Consistent with the current labeling of approved Periostat 20 mg tablets, the applicant recommends that if Oracea should be taken close to meal times, it is recommend that it be taken at least one hour prior to or two hours after meals.

Multiple Dose Pharmacokinetics:

Absorption:

The pharmacokinetics of doxycycline following multiple dose administration of Oracea was evaluated in two pharmacokinetic studies (#'s 104 and 106). The rate (C_{max}) and extent (AUC 0-24 or AUC 0-72) of absorption of doxycycline obtained in both studies were comparable. The median T_{max} of doxycycline ranged from about 0.5 hours to 4 hours in both studies, comparable to that obtained following a single dose.

In addition, the rate and extent of absorption of Oracea was found to be equivalent to that of Periostat BID following multiple dose administration for 7 days in study # 106 (N = 30). This was further demonstrated by the 90 % CI for C_{max} (101.73 to 113.20 %) and AUC (90.9 to 100.83 %) being within the 80 to 125 % range.

Excretion:

Following multiple dosing of Oracea 40 mg capsules for 7 days the mean (SD) half life of doxycycline in healthy volunteers (aged ~18-45 years old) was 23.2 (6.2) hrs in Study # 106 which is comparable to that obtained following a single dose.

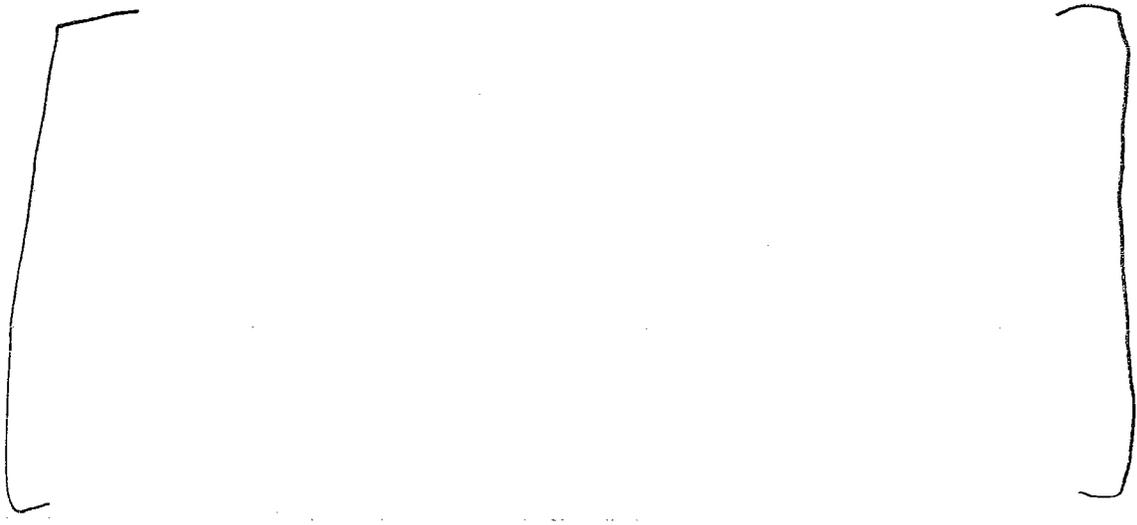
Intrinsic Factors:

Gender: The effect of gender on the pharmacokinetics of doxycycline following a single dose of Oracea was evaluated in study # 105 in 16 males and 14 female subjects under fed and fasted conditions. Female subjects had both a higher rate and extent of absorption than males. These differences are thought to be due to differences in body weight/lean body mass and are consistent with historical doxycycline PK data. The applicant has proposed to include this information in their label.

Gastric Insufficiency: The applicant included a published report by Grahnen et al (1994) in which the authors evaluate the effect of increased pH (obtained by pre-treatment with omeprazole) on the bioavailability of doxycycline monohydrate and doxycycline carrageenate in 24 healthy volunteers using an open-label, crossover, 2x2 factorial design. Following prior administration of omeprazole, doxycycline monohydrate showed a decrease in bioavailability (38 % for AUC and 45 % for C_{max}) compared to carrageenate formulation which did not show changes in bioavailability. The authors recommended that in patients with high gastric pH (e.g.

due to frequent use of H2-blockers as well as physiological achlohydria, this decreased absorption of doxycycline monohydrate may well have a clinical impact. The applicant has proposed to include this information in their label.

Dissolution:



Abimbola Adebowale, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

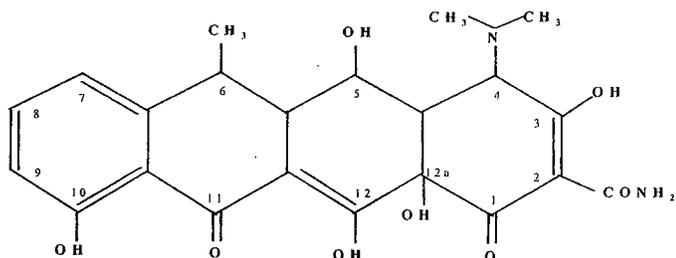
Dennis Bashaw, Pharm.D.
Team Leader
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

2. QBR

2.1 General Attributes

Physicochemical Properties of the Drug Substance:

The active pharmaceutical ingredient in Oracea is doxycycline monohydrate. The active ingredient, doxycycline monohydrate is synthetically derived from oxytetracycline. The molecular formula of doxycycline monohydrate is $C_{22}H_{24}N_2O_8 \cdot H_2O$, the molecular weight is 462.46, and the structural formula is as follows:



Doxycycline monohydrate is a light yellow to pale yellow crystalline powder that dissolves in dilute solutions of mineral acids and in solutions of alkali hydroxides and carbonates. It is slightly soluble in methanol 1 % 1M HCl, very slightly soluble in water and in alcohol, and practically insoluble in chloroform and in ether.

Therapeutic Indication (s):

The proposed indication for Oracea is to treat inflammatory lesions in patients with rosacea.

Mechanism of Action:

Rosacea is an inflammatory condition of the skin, classically presenting with flushing and/or blushing along with erythema, edema, telangiectasia, papules, pustules, and nodules of the face. The inflammatory lesions observed in patients with rosacea are, in part, manifestations of a neutrophil-mediated process. Activation of neutrophils is associated with the production of inflammatory mediators, including reactive oxygen species and nitric oxide that contribute to the inflammatory lesions. The applicant stated that research has shown that doxycycline inhibits these mediators, thereby down-regulating the pro-inflammatory response.

Proposed Dosage and Route of Administration

Oracea is intended to be taken orally, once daily in the morning.

2.2 General Clinical Pharmacology

Q. What were the design features of the clinical pharmacology and clinical studies used to support efficacy and safety?

Efficacy: Two similar Phase 3 trials, labeled COL-101-ROSE-301 (N = 251) and COL-101-ROSE-302 (N = 286), respectively, were conducted to evaluate the efficacy and safety of Oracea. The study design for both trials was identical except that a 4-week extension period without treatment was added to study 302 to assess longevity of treatment effects. Both studies were outpatient, multi-center, randomized, double-blind, placebo-controlled, parallel-group trials to evaluate the safety and efficacy of Oracea for reducing total inflammatory lesions compared with placebo. The patients were to take one capsule of study medication once daily every morning for 16 weeks. Study visits were at baseline and Weeks 3, 6, 12, 16, and in Study 302 also at week 20 (patients stopped treatment at Week 16). Patients were randomized 1:1 to Oracea or placebo.

Safety: Safety was evaluated from data obtained from the following studies that were conducted with Oracea:

- The two Phase 3 studies: COL-101-ROSE-301 and COL-101-ROSE-302 (already discussed under efficacy)
- Four pharmacokinetic (PK) studies: PERIO-DOXYSR-103, PERIO-DOXYSR-104, COL-101-SDPK-105, and COL-101-SSPK-106 (also referred to as 103, 104, 105 and 106). A brief description of the PK studies is provided in the table below:

Study ID	Objective	Design	Number of Subjects
PERIO-DOXYSR-103	To compare the bioavailability of one 40 mg capsule of Oracea QD vs. Two 20 mg Periostat® tablets BID vs. Two 20 mg Periostat® tablets QD	Open-label, randomized, three-way single-dose, crossover study with a 7 day washout between periods	18 healthy volunteers 9 males and 9 females
PERIO-DOXYSR-104	To compare the bioavailability of one 40 mg capsule of Oracea QD vs. two 20 mg Periostat® tablets BID	Open-label, randomized, two-way crossover, 7-day treatment study with a 96-hour washout between periods	14 healthy volunteers 7 males and 7 females
COL-101-SDPK-105	To evaluate the effect of food on doxycycline BA after administration of Oracea	Open-label, randomized, two-way crossover, single-dose, food-effect study with a 7-day washout between periods.	30 healthy volunteers 16 males and 14 females
COL-101-SSPK-106	To compare the pharmacokinetics and bioequivalence between one 40 mg capsule of Oracea QD and one 20 mg Periostat® tablet BID.	Open-label randomized, two-way crossover, 7 day treatment, multiple-dose study with a 7-day washout between periods	32 healthy volunteers 23 males and 9 females

Reviewer's Comments: The PK studies in the table above will be referred to as 103, 104, 105 and 106 for brevity in the rest of this QBR.

Q. What is the basis of selecting the response endpoints, i.e. clinical or pharmacodynamic end points and how were they measured in the clinical studies?

The primary efficacy endpoint identified in the protocols for the two pivotal trials was the change in total inflammatory lesion count (papules + pustules + nodules) from baseline to endpoint (Week 16). The applicant stated that this end-point was chosen because it was the most directly relevant measure to support the proposed indication for Oracea "to — inflammatory lesions in patients with rosacea". There were no pharmacodynamic endpoints evaluated in this NDA.

Q. Were the active moieties in plasma appropriately identified and measured to assess the pharmacokinetic parameters?

Yes, (See section 2.6 for details of the analytical method validation)

Q. What are the characteristics of the exposure-response relationships for efficacy or safety?

There were no exposure-response relationships evaluated in this NDA, since only one strength of Oracea is being proposed for marketing.

Q. What are the PK characteristics of the drug?

Single-Dose PK parameters

The PK of doxycycline following administration of a single dose of Oracea was evaluated in three Pharmacokinetic studies (# 103, 104 and 105). The results of these studies are reproduced in the table below:

Study ID	Pharmacokinetic Parameters mean (SD)					
	Cmax (ng/mL)	Tmax ^a (hr)	AUC 0-24 (ng.hr/mL)	AUC 0-72 (ng.hr/mL)	AUC 0-∞ (ng.hr/mL)	T _{1/2} (hr)
103 (N = 17)	523 (204.0)	2.0	5497 (1921.9)	7323 (2495.8)	7962 (2721.6)	15.1 (5.49)
104 (N = 13)	586 (159.4)	2.5	5588 (1290.5)	ND	ND	ND
105 ^b (N = 30)	510 (220.7)	3.0	ND	8189 (2999.1)	9227 (3212.8)	21.2 (7.64)

a median (range) shown for Tmax; ND = not determined
 b fasted treatment leg only

Reviewer's Comments: The single dose pharmacokinetic parameters obtained in all three studies were comparable.

Multiple-Dose PK Parameters:

The PK of Oracea capsules following administration of multiple doses for 7 days were evaluated in two Pharmacokinetic studies (#104 and 106). The results of these studies are reproduced in the table below:

Study ID	Pharmacokinetic Parameters mean (SD)				
	Cmax (ng/mL)	Tmax ^a (hr)	AUC 0-24 (ng.hr/mL)	AUC 0-72 (ng.hr/mL)	T _{1/2} (hr)
104 (N = 13)	602 (177.6)	2.0	7230 (1963.9)	ND	ND
106 (N = 30)	600 (194.2)	2.0	ND	7543 (2443.9)	23.2 (6.2)

a median (range) shown for Tmax; ND = not determined

Reviewer's Comments: Cmax and Tmax are comparable for both studies and AUC is somewhat comparable. The PK parameters obtained after multiple dosing are somewhat comparable to that obtained following single dosing if one takes the variability into account.

Q. Is the single dose pharmacokinetics of Oracea comparable to that of a currently marketed immediate release drug product (Periostat 20 mg tablets) that contains doxycycline?

No it is not. The data from study # 103 and 104 indicated that following a single dose, the systemic exposure of doxycycline from Oracea is higher than that of Periostat BID. In study # PERIO-DOXYSR-103 (N=17), the applicant compared the pharmacokinetics of doxycycline after a single dose administration of Oracea, to currently marketed Periostat 20 mg BID and 40 mg QD in healthy volunteers. Inserted below is a graph showing the plasma concentration time profiles for the three treatments:

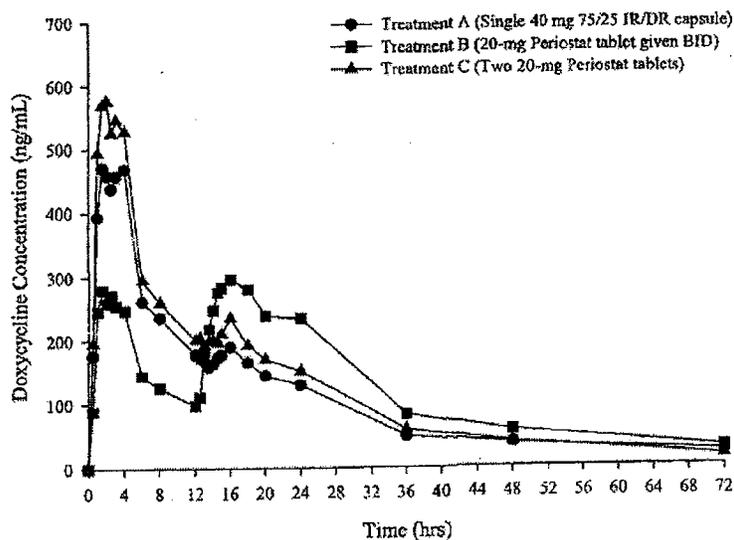


Figure 14.2.1-1. Mean Plasma Doxycycline Concentration versus Time Profile in the Normal Scale.

Reviewer's Comments: The graphs above indicate that Treatment A (Oracea 40 mg) had a systemic exposure that was higher than that obtained for Treatment B (Periostat® 1x 20 mg) and lower than that obtained for Treatment C (Periostat® 2x 20 mg). Graph above demonstrates that Oracea shows some extended release but not delayed release properties.

Table 2.7.1-2 PERIO-DOXYSR-103: Pharmacokinetic Results for Doxycycline

Treatment	Pharmacokinetic Parameters for Doxycycline					
	C _{max} (ng/mL)	t _{max} ^a (hr)	AUC ₀₋₂₄ (ng·hr/mL)	AUC _{0-t} (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
A (Oracea™)						
Mean	523	2.0	5497	7323	7962	15.1
SD	204.0		1921.9	2495.8	2721.6	5.49
B (Periostat® BID)						
Mean	363	13.5	4931	8321	9229	16.0
SD	185.7		1876.9	3553.6	3877.6	4.66
C (2 Periostat® once)						
Mean	623	1.5	6373	8745	9570	20.8
SD	245.9		2476.0	3789.2	4050.7	14.52

Source: Table 11.4.1.1-1 (Module 5, volume 1.1, page 52)
^a Median (range) shown for t_{max}.

Reviewer's Comments: The PK parameters show that Treatment C (Periostat 2 x 20 mg at once) had the highest value for mean C_{max} and AUC_{inf} in comparison to Treatments A (Oracea) and B (Periostat 1 x 20 mg). Treatment A had a higher C_{max} and AUC₀₋₂₄, but lower AUC_{0-t} and AUC_{0-∞} than treatment B. Therefore the results for AUC were not consistent. The T_{max} was comparable for Treatment A and C. Applicant stated that the relatively high median T_{max} value for treatment B could be attributed to the T_{max} occurring during the PM dose of the 12-hour BID dosing regimen. Mean T_{1/2} values were similar across treatments.

Table 2.7.1-3 PERIO-DOXYSR-103: Statistical Results of Relative Bioavailability for Doxycycline

Comparison of Treatments	Parameter	Test Mean ^a	Reference Mean ^a	Test/Reference ^b	90% Confidence Interval ^c
A (Oracea TM) to B (Periostat [®] BID)	ln(C _{max})	481	328	147	(125, 172)
	ln(AUC ₀₋₂₄)	5175	4622	112	(97.7, 128)
	ln(AUC _{0-t})	6965	7735	90.0	(76.2, 106)
	ln(AUC _{0-∞})	7567	8592	88.1	(75.7, 102)
A (Oracea TM) to C (2 Periostat [®] once)	ln(C _{max})	481	545	88.2	(75.3, 103)
	ln(AUC ₀₋₂₄)	5175	5678	91.1	(79.6, 104)
	ln(AUC _{0-t})	6965	7620	91.4	(77.3, 108)
	ln(AUC _{0-∞})	7567	8441	89.6	(77.0, 104)
C (2 Periostat [®] once) to B (Periostat [®] BID)	ln(C _{max})	545	328	166	(142, 195)
	ln(AUC ₀₋₂₄)	5678	4622	123	(107, 141)
	ln(AUC _{0-t})	7620	7735	98.5	(83.4, 116)
	ln(AUC _{0-∞})	8441	8592	98.2	(84.4, 114)

Reviewer's Comments: Consistent with the PK results above, the statistical comparisons indicated that the rate and extent of absorption of doxycycline from Oracea (Treatment A) was not equivalent to that of Periostat[®] BID (Treatment B) or Periostat 40 mg at once (Treatment C). The 90% CI for ln C_{max} and ln AUC (except AUC_{0-t} and AUC_{0-∞} for comparison of Treatment B and C) were all outside the 80% to 125% range.

The applicant stated that the relatively small sample size of 17 subjects should be taken into consideration in evaluating these results. This reviewer believes that another source of error could have been due to that fact that a large number of samples had to be re-assayed because they yielded concentration levels that were above the range of the calibration curve. Although the dilution was validated, however, diluting the samples to bring them within the range of the standard curve could have introduced another source of error.

In study # PERIO-DOXYSR-104 (N = 13) the applicant compared the systemic exposure of doxycycline after a multiple dose (7 days) administration of Oracea, to currently marketed Periostat 20 mg BID in healthy volunteers. In this study the relative bioavailability of doxycycline on Day 1 and Day 7 were evaluated. Reproduced in the table below are the Day 1 pharmacokinetic results.

Table: PERIO-DOXYSR-104: PK and Statistical Results for Doxycycline

PK Parameter	Treatment A (Oracea)	Treatment B (Periostat BID)	90% Confidence* Interval
C _{max} (ng/mL)	586 (159.4)	343 (129.2)	(147, 203)
AUC (0-24) (ng.hr/mL)	5588 (1290.5)	4399 (1358.7)	(114, 144)
T _{max} (hr) ^a	2.50 (1.0, 4.0)	15.0 (0.5, 23.9)	NA

^a T_{max} = median (range); * 90% CI on natural log transformed parameters; NA = not applicable

Reviewer's Comments: Following a single dose, the data obtained was consistent with that of study # 103 in that the rate and extent of absorption of doxycycline was higher from Oracea when compared to Periostat BID. The 90% CI for ln Cmax and ln AUC were also outside the 80% to 125 % range. Applicant stated that the relatively high median Tmax value for treatment B could be attributed to the Tmax occurring during the PM dose of the 12-hour BID dosing regimen.

The data from study # 103 and 104 indicate that following a single dose, the systemic exposure of doxycycline from Oracea is higher than that of Periostat BID, indicating that safety may be a concern from a clinical perspective (preliminary review of the safety data indicated that there were no serious adverse events reported in these two studies, however this is currently under review by the medical reviewer). Since this medication is intended for chronic dosing this may not be a concern if the systemic exposure following multiple dose administration is similar.

Q. Is the steady-state pharmacokinetics of Oracea comparable to that of a currently marketed immediate release drug product (Periostat 20 mg tablets) that contains doxycycline?

Yes it is. In study # COL-101-SSPK-106 (N = 30), the rate and extent of absorption of Oracea 40 mg QD administered for 7 days versus Periostat® tablets 20 mg BID administered for 7 days in healthy volunteers was evaluated. Inserted below is a graph showing the Day 7 plasma concentration-time profiles of both treatments.

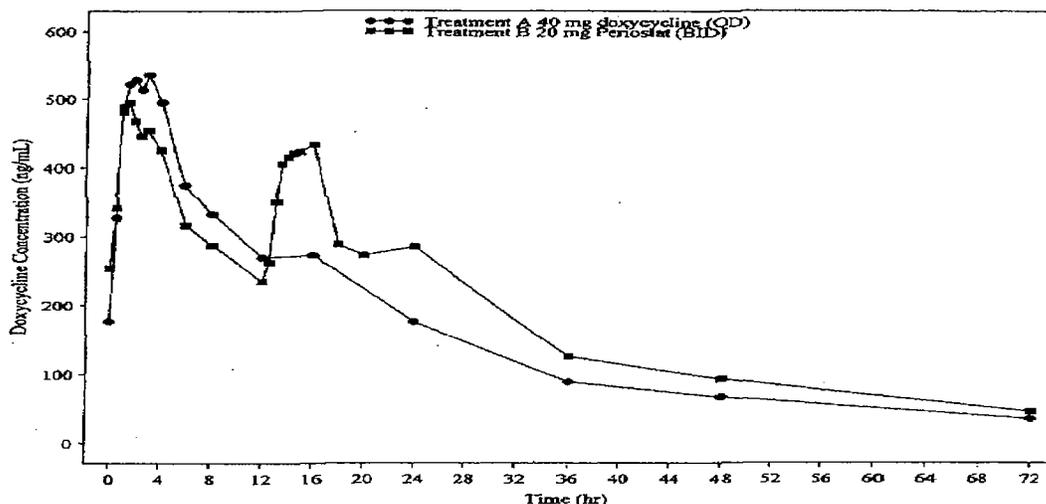


Figure 14.2.1-1 Mean Plasma Doxycycline Concentration on Day 7 versus Time Profile in the Normal Scale

The arithmetic mean PK parameters on day 7 are summarized in the table below:

Table 2.7.1-9 COL-101-SSPK-106: Arithmetic Mean (SD) Pharmacokinetic Parameters for Doxycycline

Doxycycline PK Parameter ^a	A (Oracea™ QD)	B (Periostat® BID)
C _{max} (ng/mL)	600 (194.2)	565 (233.3)
t _{max} (hr)	2.00 (1.0, 4.0)	2.25 (1.00, 12.0)
AUC _{ss} (ng·hr/mL)	7543 (2443.9)	8040 (3288.8)

a: values are mean (SD) except for median (range) for Tmax

Reviewer's Comments: Doxycycline had a median Tmax value of approximately 2 hours after both treatments A and B. Treatment A (Oracea) had a higher arithmetic mean for Cmax and a lower mean AUC value for doxycycline relative to Treatment B (Periostat® tablets) which is consistent with the graphical representation above.

Table 2.7.1-10 COL-101-SSPK-106: Statistical Analysis of Pharmacokinetic Data

Doxycycline PK Parameter	Test Least Squares Mean (Treatment A, Oracea™)	Reference Least Squares Mean (Treatment B, Periostat® BID)	Test/ Reference	90% Confidence Interval
AUC _{0-∞} (ng·hr/mL)	7216	7537	95.7	(90.90, 100.83)
C _{max} (ng/mL)	571	532	107	(101.73, 113.20)
C _{min} (ng/mL)	153	202	75.7	(70.78, 80.87)

Reviewer's Comments: The data in the table above indicates that Treatment A and Treatment B were equivalent at steady state because the 90% confidence intervals for ln (Cmax) and ln (AUC_{0-∞}) were contained within the 80% to 125% range. The Cmin for Treatment A was less than that of Treatment B. The clinical relevance of this finding in terms of efficacy is unknown.

2.3 Intrinsic Factors

How does the systemic exposure change with various intrinsic factors?

Gender Effect: The applicant evaluated the effect of gender on the pharmacokinetics of doxycycline after a single dose administration of Oracea in study # COL-101-SDPK-105 in 16 males and 14 females under fed and fasted conditions. Inserted below is a table showing the results of the gender analysis:

Table 2.7.1-8 COL-101-SDPK-105: Statistical Analysis of Pharmacokinetic Data -- Gender Effect

Doxycycline PK Parameter	Treatment	Gender	Least Squares Mean	Gender-by-Treatment P-value ^a	Pairwise P-value ^a			Gender P-value ^b
					A-Male	B-Female	B-Male	
C _{max} (ng/mL)	A (fasted)	Female	657	0.0076	<0.0001	<0.0001	<0.0001	NA
		Male	351				<0.0001	
	B (fed)	Female	320			0.3210	0.0010	NA
		Male	227					
AUC _{0-t} (ng·hr/mL)	A (fasted)	Female	9715	0.2259	NA	NA	NA	0.0003
		Male	6303				NA	
	B (fed)	Female	7252			NA	NA	0.0010
		Male	5229				NA	
AUC _{0-∞} (ng·hr/mL)	A (fasted)	Female	10614	0.3415	NA	NA	NA	0.0019
		Male	7357				NA	
	B (fed)	Female	8099			NA	NA	0.0043
		Male	6086				NA	

Consistent with historical doxycycline PK data (and as reflected in the product labeling for Periostat®), a significant gender effect was observed on the rate (Cmax) and extent (AUC) of doxycycline absorption from Oracea. Female subjects had both a higher rate and extent of absorption than males. Further, for the rate of doxycycline absorption, a gender-by-treatment

effect was observed, with a significantly higher C_{max} for fasted female subjects compared with fed female subjects and, fasted or fed male subjects. These differences are thought to be due to differences in body weight/lean body mass.

Reviewer's Comments:

The applicant has proposed to include this data in the label under "special populations" after clinical studies" as follows:

Gender: The pharmacokinetics of ORACEA was compared in 16 males and 14 females under fed and fasted conditions.

However, this reviewer is proposing some revision to the label to be consistent with the approved label in Periostat tablets (see section 3 for labeling recommendations)

[]

The published report by Grahnen et al (1994) evaluated the effect of increased gastric pH (obtained by pre-treatment with omeprazole) on the bioavailability of doxycycline monohydrate and doxycycline carrageenate in 24 healthy volunteers, using an open, randomized, four-treatment, four-period, crossover, 2 x 2 factorial design. Each subject received a single dose of 100 mg of each of the doxycycline formulations with and without pre-treatment with omeprazole (40 mg daily for 7 days). There was a one week wash-out period between sessions. Blood samples were obtained after dosing at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h. The plasma concentrations of doxycycline were determined by a modified HPLC method with UV detection. The limit of quantitation was 0.05 mcg/mL.

Results:

The authors concluded that a statistically significant difference in kinetics was observed between the two formulations of doxycycline, as the doxycycline formulation was shown to have decreased bioavailability at high gastric pH, and the new formulation doxycycline carragenate had unchanged bioavailability at high pH. Basically, the two formulations had a comparable rate and extent of absorption without omeprazole pre-treatment. After omeprazole, the monohydrate showed a decrease in bioavailability (38% for AUC and 45% for C_{max}) compared to the carrageenate formulation, which was not affected by prior administration of omeprazole. Many of the subjects (about 40 %) did not reach a therapeutic plasma level of doxycycline (0.6 mcg/mL) during the combination of omeprazole and doxycycline monohydrate, and most adverse events (mainly gastrointestinal) were reported after this combination. The authors stated that although pH was not monitored during the study, the effect of 1 week of pre-treatment with omeprazole is very probably related to achlorhydria.

¹ Grahnen A, Olsson B, Johansson G, et al. Doxycycline carrageenate-an improved formulation providing more reliable absorption and plasma concentrations at high gastric pH than doxycycline monohydrate. Eur J Clin Pharmacol 1994; 46: 143-146.

Based on the aforementioned, the authors recommended that, as large populations of patients have a high gastric pH due to frequent use of H2-blockers, proton pump inhibitors and antacids, as well as to physiological achlorhydria, the decreased absorption of doxycycline monohydrate may well have a clinical impact, for example when the patients are treated with tetracyclines for an infection.

Reviewer's Comments: Although the study was not actually conducted in patients with gastric insufficiency and the formulation used in this study is not the same as the proposed formulation the doxycycline salt is the same. Also there is also the potential for increased gastric pH causing an alteration in the release of doxycycline from the DR beads. Therefore, it is recommended that the proposed label be modified as recommended in Section 3 of this review.

2.4 Extrinsic Factors

Drug-Drug Interactions:

The applicant included wording from Periostat label as well as the following additions (bolded italics) to the label in the Precautions section for Oracea:

Drug Interactions: "Absorption of tetracyclines is impaired by bismuth subsalicylate, *proton pump inhibitors*,¹ antacids and nutritional supplements containing aluminum, calcium, magnesium, or iron".

Reviewer's Comments: Applicant claimed proton pump inhibitors were added based on the published study by Grahn et al (1994) described above under gastric insufficiency.

2.5 General Biopharmaceutics

What is the in vivo relationship between the to-be-marketed formulation and the pivotal clinical trial formulation(s)?

The applicant stated that the same formulation of Oracea was used for all four PK studies and the two Phase 3 studies, and it is the formulation proposed for marketing. Inserted below is a table showing the quantitative composition of Oracea™ capsules.

Table 3.2.P.1-6: Quantitative Composition (mg/capsule and kg/batch) of Oracea™

Component	Mg/Capsule	Kg/Batch	%
Doxycycline Monohydrate, USP/NF			
Hypromellose, — USP/NF			
Methacrylic Acid Copolymer — USP/NF			
Triethyl Citrate, USP/NF			
Talc, USP/NF			
Sugar Spheres, — USP/NF			
Purified Water, USP/NF			
Hard Gelatin Capsule #2, Beige Opaque			
Total^a			

^a Total rounded to nearest whole number.

Q. What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

Food was observed to decrease the bioavailability of doxycycline after a single dose of Oracea 40 mg capsule. The applicant evaluated the effect of food on the pharmacokinetics of a single dose of Oracea (40 mg) in healthy male and female subjects in study # COL-101-SDPK-105, a randomized, two-way crossover study in 30 subjects. Inserted below are the graphical representation and the summary table of the mean (SD) PK parameters obtained after a single dose of Oracea capsules.

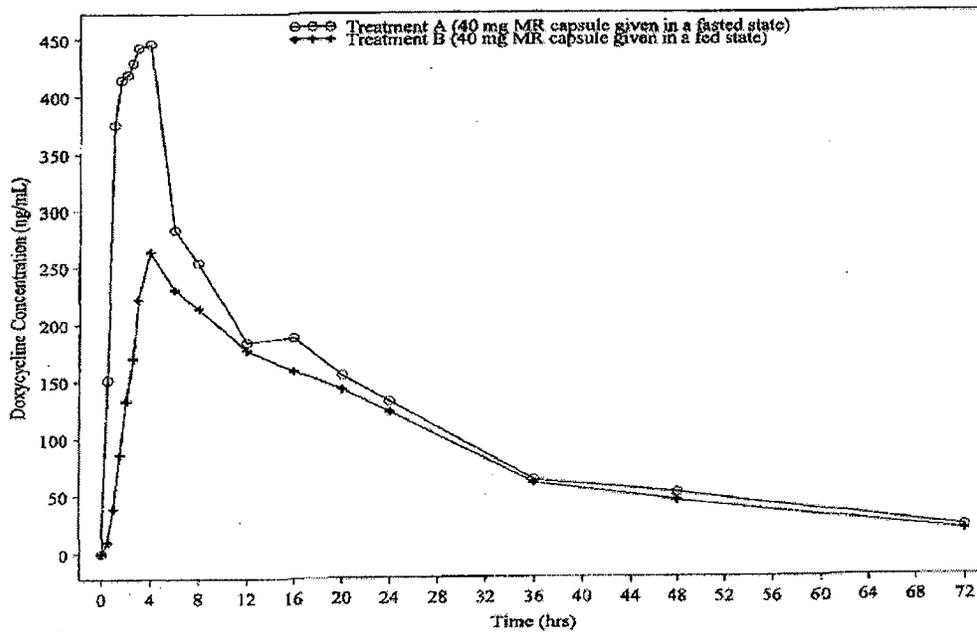


Figure 14.2.1-1 Mean Plasma Doxycycline Concentration versus Time Profile in the Normal Scale

Table 2.7.1-6 COL-101-SDPK-105: Arithmetic Mean (SD) Pharmacokinetic Parameters for Doxycycline

Doxycycline PK Parameter ^a	A (Oracea™ fasted state)	B (Oracea™ fed state)
C _{max} (ng/mL)	510 (220.7)	280 (98.2)
t _{max} (hr)	3.00 (1.0, 4.1)	4.00 (2.50, 16.0)
AUC _{0-t} (ng·hr/mL)	8189 (2999.1)	6419 (2282.9)
AUC _{0-∞} (ng·hr/mL)	9227 (3212.8)	7298 (2459.3)
t _{1/2} (hr)	21.2 (7.64)	23.5 (9.16)

a: values are mean (SD) except for median (range) for T_{max}

Table 2.7.1-7 COL-101-SDPK-105: Statistical Analysis of Pharmacokinetic Data

Doxycycline PK Parameter	Test Least Squares Mean (Treatment B)	Reference Least Squares Mean (Treatment A)	Test/Reference	90% Confidence Interval	T _n P ²
C _{max} (ng/mL)	266	470	56.6	(51.53, 62.06)	
AUC _{0-t} (ng-hr/mL)	6091	7713	79.0	(73.46, 84.90)	
AUC _{0-∞} (ng-hr/mL)	6954	8730	79.7	(74.27, 85.45)	
K _e (1/hr)	0.0334	0.0359	93.2	(81.47, 104.95)	
t _{max} (hr)	4.00	3.00	NA	NA	< (

Reviewer's Comments: The data in the graphs and tables above indicate that the rate and extent of doxycycline absorption after a single dose of ORACEA were lower for Treatment B (fed) in comparison to Treatment A (fasted). The 90% confidence intervals for ln (C_{max}), ln (AUC_{0-t}), and ln (AUC_{0-∞}) were outside the 80% to 125% range, indicating that the two treatments were dissimilar. There was a delay of about 1 hour for the mean T_{max} in the fed state compared to the fasted state. In addition the T_{max} was much more variable (range of _____ in the fed state compared to the fasted state (range of _____).

Q. What dosing recommendation should be made, if any regarding the administration of the product in relation to meals?

The applicant has proposed the following wording in the label:

Dosage and Administration:

Reviewer's Comments: This proposed labeling is generally consistent with the current label for Periostat, however the sponsor will need to modify the wording under absorption. It is not clear how the sponsor came up with the values of _____ it appears it was based on the least square means and not the arithmetic means). (see section 3 for this reviewer's labeling recommendations)

Q. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The proposed dissolution method is acceptable however the specifications need to be tightened to ensure consistency in the quality of the product.

Proposed Dissolution Method:

Apparatus	USP Dissolution Apparatus II (Paddles)
Media	[]
Sampling Time Points	
Agitation Speed	
Temperature	
Specifications	

Dissolution Method Development: To ensure the drug contained in the DR beads is not released in the acidic stomach environment a

Agitation Study: Rotation speeds of — and — rpm were evaluated using the dissolution media and conditions in the table above.

Figure 2: Agitation Study,

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

The applicant may also want to propose a specification for the _____ time point during the _____ since at least _____ if the drug product is dissolved during this time.

2.6 Analytical

Q. Were the analytical methods used for the determination of _____ in biological fluids validated?

A high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection was used for the determination of doxycycline in human plasma. The method validation results indicated acceptable precision, reproducibility, accuracy, sensitivity and selectivity. The validation parameters of the method are reproduced in the table below:

Analytical Method Validation

Compound	Doxycycline
Internal Standard (IS)	C_____
Matrix	Plasma
Standard curve range	15 to 1200 ng/mL (r = 0.999, n = 3)
Sensitivity (LOQ)	15 ng/mL (%CV = 3.5, n = 6)
Selectivity	No interfering peaks were observed at the retention times of doxycycline and the IS.
Stability	Following 3 freeze-thaw cycles in plasma @ approximately -20°C, < 8.4 % degradation was observed
Mean Recovery % (%CV)	61.7 %-68 % (doxycycline) and 71.9 %-75.2 % (IS)

Mean intra-assay precision and accuracy data based upon the percent relative standard deviation (%RSD) and percent Deviation of Mean from Theoretical (% DMT) of quality control samples are summarized in the table below:

	QC 15.0 ng/mL (LLOQ)	QC 45.0 ng/mL (Low)	QC 600 ng/mL (Mid)	QC 900 ng/mL (High)	*QC 4500 ng/mL (Dilution)
n	6	6	6	6	6
Mean (ng/mL)	16.4	48.3	608	899	4720
Precision (%RSD)	3.5	1.7	2.4	1.0	1.2
Accuracy (%DMT)	9.3	7.3	1.3	-0.1	4.9

* Analyzed after 10-fold dilution with analyte-free matrix.

Mean inter-assay precision and accuracy data based upon the percent relative standard deviation (%RSD) and percent Deviation of Mean from Theoretical (% DMT) of quality control samples are summarized in the table below:

	QC 45.0 ng/mL (Low)	QC 600 ng/mL (Mid)	QC 900 ng/mL (High)
n	18	18	18
Mean (ng/mL)	47.9	617	911
Precision (%RSD)	3.0	1.8	2.3
Accuracy (%DMT)	6.4	2.8	1.2

3 Labeling Recommendations:

Pharmacokinetics

Reviewer's Comments: Applicant needs to include some information on the variability of the pharmacokinetic parameters as shown in bolded italics Standard deviation for all except Tmax that shows range):

Table 1. Pharmacokinetic Parameters [Mean (\pm SD)] for ORACEA

	n	C _{max} * (ng/mL)	T _{max} ⁺ (hr)	AUC _{0-∞} * (ng·hr/mL)	t _{1/2} * (hr)
Single Dose 40 mg controlled- release capsules	30	510 ± 220.7	3.00	9227 ± 3212.8	21.2 ± 7.64
Steady-State [#] 40 mg controlled-release capsules	31	600 ± 194.2	2.00	7543 ± 2443.9	23.2 ± 6.2

Sponsor's Proposed Label:



Reviewer's revised recommendation is as follows:

- Absorption:** In a single-dose *food-effect* study involving **administration of ORACEA** to healthy volunteers, concomitant administration of ORACEA with a 1000 calorie, high-fat, high-protein meal that included dairy products, resulted in a decrease in **the rate and extent of absorption (C_{max} and AUC) by about 45 % and 22 %, respectively,** compared to dosing under fasted conditions. **This decrease in systemic exposure can be clinically significant, and therefore if ORACEA is taken close to meal times, it is recommended that it be taken at least one hour prior to or two hours after meals.**

- **Dosage and Administration:** Oracea should be taken once daily in the morning *on an empty stomach.* ~~preferably~~ at least one hour prior to or two hours after meals.

Sponsor's Proposed Label:

Gender: The pharmacokinetics of ORACEA was compared in 16 males and 14 females under fed and fasted conditions.

Reviewer's revised recommendation is as follows:

- Special populations sections should be placed under "Clinical Pharmacology"

- **Gender:**

[]

Sponsor's Proposed Label;

Gastric Insufficiency:

Reviewer's revised recommendation is as follows:

Gastric Insufficiency:

4 Appendix

- 4.1 Pharmacometrics Consult: None required since there was no PK/PD or POPPK data submitted.
- 4.2 Proposed Package Insert:

Oracea™
(doxycycline capsules) 40 mg

DESCRIPTION

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9 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1a

Storage: All products are to be stored at controlled room temperatures of 15°C - 30°C (59°F - 86°F) and dispensed in tight, light-resistant containers (USP).

Rx Only

ORACEA is a trademark of CollaGenex Pharmaceuticals, Inc., Newtown, PA, 18940

Manufactured by:
CardinalHealth
Winchester, KY 40391

Marketed by:
CollaGenex Pharmaceuticals, Inc.
Newtown, PA, 18940

4.3 Individual Study Reviews:
Study Number: COL-101-SSPK-106

Title of Study: An Open-Label, Randomized, Two-way Crossover, Multiple-Dose Pharmacokinetic Study to Compare 40 mg Doxycycline as a Once-a-Day (QD), Modified-Release Dosage Form Administered for 7 days Versus Periostat® tablets (20-mg) Administered Orally Every 12 Hours (BID) for 7 Days in Normal, Healthy, Non-Smoking Male and Female Volunteers
Principal Investigator (s): _____
Study Center (s): _____
Objectives: To compare the rate and extent of absorption of doxycycline at steady state for the test treatment (Treatment A: Doxycycline controlled-release 40-mg capsule administered QD) to that of the reference treatment (Treatment B Periostat® 20-mg tablet administered orally BID).
Study Population: 32 healthy male and female subjects enrolled in the study, and 30 subjects completed the study.
Study Design: Open-Label, Randomized, Two-way Crossover, Multiple-Dose, Single-Center Study
Study Period: 05 January 2005 to 28 January 2005
Investigational Product (s): Doxycycline _____ (Oracea), 40-mg capsule, Lot # 0400289 manufactured by Cardinal Health, KY, expired 30 September 2005 [Treatment A (Test)] and, Periostat®, two 20-mg tablets, each containing 23 mg doxycycline hyclate (equivalent to 20 mg doxycycline), Lot # B04045A, expires January 2007 [Treatment B (Reference)]
Drug Administration: Subjects were randomly assigned to 1 of 2 sequences (i.e. I: A/B or II: B/A). Oracea 40mg capsule (TX A) was administered in the morning (QD) for 7 days and Periostat tablets (TX B) was administered BID, 12 hours apart for 7 days. Each dose was administered with 240 mLs of water. For the morning dose fasting was for at least 7 hours before through 4 hours post dose. For the evening dose (TX B) and PM time-point (TX A), fasting was from at least 2 hours before through 4 hours post-dose or time-point. Wash out period was 7 days for Sequence I and 6.5 days for Sequence II.

PK Sampling Scheme: 7 mLs of blood samples were collected on Study Day 7 for TX A & B as follows:

TX A: pre-dose (0 hour) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours postdose

TX B: pre-dose (0 hour) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 (pre-PM dose), 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 20, 24, 36, 48 and 72 hours post-AM dose

Both treatments: trough blood samples prior to the AM dose on Study Days 1, 4, 5, 6 and 7 and a sample before the PM dose for TX B

Analytical Methods: HPLC with UV detection

PK data Analysis: C_{max}, C_{min}, AUC_{0-∞}, K_e and T_{1/2} were calculated for all treatments. T_{max} for TX B was normalized to the time of dosing if it occurred after the second (PM) dose. Steady state was assessed separately for each treatment group by comparing trough plasma concentrations on days 4, 5, 6, and 7.

Reviewer's Comment: Applicant stated that trough data taken on Day 7, Hour 12 was excluded from the steady state statistical analysis to eliminate the impact of diurnal variation. It is not clear how this was established. Applicant should have included that time-point in the statistical analyses and compared with and without analyses to determine if there was truly an effect.

Statistical Analysis: ANOVA and generation of 90 % CI for ratios of T/R. Criteria used for comparable absorption was that CI was contained within the 80 % to 125 % range.

Results:

Demographics:

Parameter/Statistic	N = 32
Age (years) [Mean ± SD]	29 ± 8.4
Range	[18-45]
Gender: Male / Female	23 Males/ 9 Females
Ethnic Origin	
Black	4
Caucasian	24
Asian	1
Hispanic	2
American Indian/Alaskan Native	1
Height (cm) [Mean ± SD]	175 ± 10.63
Range	[146.5-190]
Weight (kg) [Mean ± SD]	74.9 ± 12.21
Range	[47.6-98.2]

Two subjects withdrew consent before the conclusion of the study. Subject # 032 withdrew consent for the study on Day 4 of Period 1 due to AEs of nausea, headache, decreased appetite, and lower abdominal pain. Applicant stated that and was not included in any inferential statistics. Subject # 010 withdrew consent for the study prior to Day 7 of Period 2, however, this subject's period 1 data was included in the formal statistical analyses.

Reviewer's Comment: Applicant stated that all of these AEs experienced by Subject # 032 were judged to be mild in severity. Clinical reviewer is currently evaluating this information.

Pharmacokinetics

Plasma Concentration VS. Time data:

Reviewer's Comments: Graphs shows that Oracea demonstrates (SOME/MODEST) extended release properties, not delayed release.

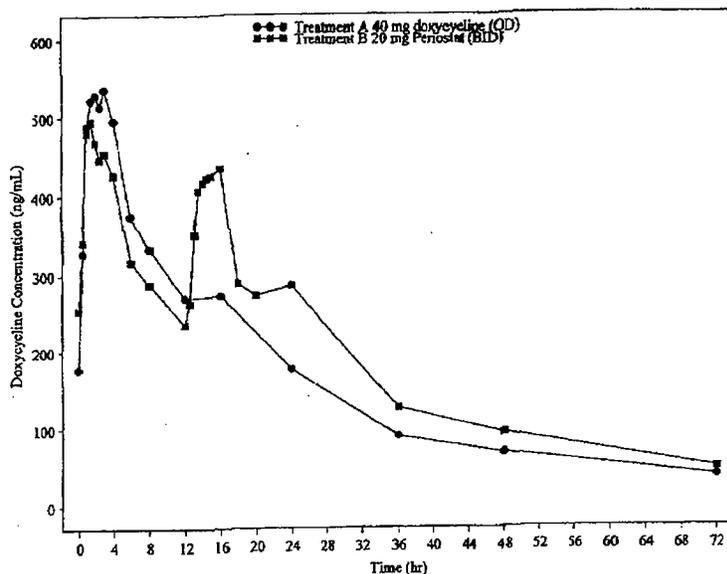


Figure 14.2.1-1 Mean Plasma Doxycycline Concentration on Day 7 versus Time Profile in the Normal Scale

Pharmacokinetic Parameters:

Table 11.c Summary Table of Pharmacokinetic Parameters for Doxycycline

Day	Mean PK Parameters ^a	Units	Treatment ^b	
			A	B
7	C _{max}	(ng/mL)	600 (194.2)	565 (233.3)
	t _{max}	(hr)	2.00 (1.00, 4.02)	2.25 (1.00, 12.0)
	AUC _{SS}	(ng·hr/mL)	7543 (2443.9)	8040 (3288.8)

^a Mean (standard deviation) shown for C_{max} and AUC_{SS}. Median (minimum, maximum) shown for t_{max}.

^b Treatment A = 40 mg doxycycline as a controlled-release dosage form administered orally QD; Treatment B = one 20-mg Periostat[®] tablet administered orally BID.

Applicant's Summary

The results of Table 11.c. indicated rapid absorption of doxycycline after both Treatments A and B with a median t_{max} of approximately 2 hours. After reaching C_{max}, the plasma concentrations of doxycycline slowly declined with an arithmetic mean t_{1/2} of 23.2 (± 6.2) hours for TX A and 21.4 (± 4.38) hours for TX B. There was no marked difference in t_{1/2} between the two treatments.

Treatment A had slightly higher mean C_{max} and a lower arithmetic mean AUC_{SS} value for doxycycline relative to Treatment B, but differences were not marked. It was observed from the arithmetic mean plasma concentration-time plot for treatment B, that the arithmetic mean C_{max} after the first dose was often higher than the arithmetic mean C_{max} after the second dose. The reason for this was not clear, but it may have been due to diurnal variation in gastrointestinal absorption, which directly affects the PK of doxycycline. It was also observed that the arithmetic plasma concentration for Treatment A had, in general, lower variability than Treatment B. The % CV for C_{max} and AUC_{SS} for Treatment A was 32.4 % (for both

parameters) compared to 41.3 and 40.9 %, respectively, for Treatment B.

Reviewer's Comments: In addition Tmax for TXA had a lower variability than TXB also. Therefore the absorption was more variable with TXB.

Assessment of SS:

Table 11.b Trough Concentration (ng/mL) Data for Doxycycline

Treatment	Plasma Concentration (ng/mL)				
	Day 1	Day 4	Day 5	Day 6	Day 7 AM
A	0 (0)	183 (93.2)	182 (75.5)	181 (77.6)	177 (76.3)
B	0 (0)	258 (99.5)	269 (118.8)	253 (101.8)	251 (145.0)

Reviewer's Comments: Based on data above, SS for doxyxcycline was generally achieved by Day 4 for both treatments. In addition the statistical results for the assessment of SS indicated that p-value testing for equality among day arithmetic means was not significant ($P > 0.05$) for treatment A and B, supporting the attainment of SS.

Statistical Comparison of Pharmacokinetic Parameters:

Table 11.d Summary Table of Statistical Results of the Rate and Extent of Absorption of Doxycycline

Treatment A Relative to Treatment B

Parameter	Units	Test Least	Reference Least	Test/Reference	90%
		Squares Mean (Treatment A)	Squares Mean (Treatment B)		Confidence Interval
AUC _{SS}	ng-hr/mL	7216	7537	95.7	(90.90, 100.83)
C _{max}	ng/mL	571	532	107	(101.73, 113.20)
C _{min}	ng/mL	153	202	75.7	(70.78, 80.87)

Reviewer's Comments: For the comparison of Treatment A and Treatment B, the 90% CI for natural logarithms of Cmax and AUCss were contained within the 80 to 125 % range. Therefore the two treatments are equivalent with regards to the rate and extent of doxycycline absorption at steady state. The numerical values indicates that the Cmin values were higher for treatment B compared to Treatment A on Day 7, and this was further supported by the statistical analyses that showed that the 90 % CI for natural logarithms of Cmin were outside the 80 to 125 % range.

Applicant's Overall Conclusion:

Doxycycline Cmax and AUCss were similar for Treatment A in comparison to Treatment B on Day 7, indicating that the 2 treatments were equivalent regarding the rate and extent of doxycycline absorption at steady state. Doxycycline Cmin was higher for Treatment B in comparison to Treatment A on Day 7.

Analytical Method Validation

Compound	Doxycycline
Internal Standard	
Matrix	Plasma
Accuracy (DMT%) Between-Day	-8.8 to -0.4

Precision (CV %) <i>Between-Day</i>	5.7 to 7.2 %
Standard curve range	15 to 1200 ng/mL (r = 0.999, n = 26)
Sensitivity (LOQ)	15 ng/mL (%CV = 6.3, n = 25)
Selectivity	No interfering peaks at retention times of interest
Mean Recovery % (%CV)	
Stability	After storage @-10 to -30°C for 40 days, degradation was
Conclusions	Method Acceptable

DMT = Deviation of mean from theoretical

Labeling Claims from Study: Mean values of C_{max}, T_{max}, AUC_{0-∞} and t_{1/2} for Oracea on Day 7 was included in Table 1 entitled "PK Parameters for Oracea" in the label.

Reviewer's Comments: Applicant needs to include some measure of variability such as SD in the label as well.

Study Number: COL-101-SDPK-105

Title of Study: An Open-Label, Randomized, Two-way Crossover, Single-Dose Food-Effect Pharmacokinetic Study of a 40 mg Doxycycline Modified-Release Dosage Form Administered Orally to Normal, Healthy, Non-Smoking Male and Female Volunteers
Principal Investigator (s)
Study Center (s):
Objectives: To evaluate the effect of food on the rate and extent of absorption from a 40-mg doxycycline controlled-release (formerly described as modified release) oral dosage form administered as a single dose in healthy adult subjects.
Study Population Demographics: 30 healthy male and female subjects entered and completed the study
Study Design: Open-Label, Randomized, Two-way Crossover, Single-Dose, Single-Center Food-Effect Study
Study Period: 19 th January 2005 to 30 th January 2005
Investigational Product (s): Doxycycline _____ (Oracea), 40-mg capsule, Lot # 0400289 manufactured by Cardinal Health, KY, expired 30 September 2005.
Drug Administration: Subjects were randomly assigned to 1 of 2 sequences (i.e. I: A/B or II: B/A). Oracea 40mg capsule (TX A) was administered in the morning to subjects in the fasted state and, Oracea 40mg capsule (TX B) was administered in the morning to subjects in the fed state. Each dose was administered with 240 mLs of water. For the fasted state, fasting was for at least 10 hours before through 4 hours post dose. For the fed state dosing was ~ 5 minutes after consumption of a FDA-standardized high-fat content breakfast eaten within 25 minutes. Wash out period was 7 days between period 1 and 2 doses. Standardized FDA high-fat breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz. of hash brown potatoes and 8 oz. (240 mL) of whole milk.
PK Sampling Scheme: 7 mLs of blood samples were collected on Day 1 for both treatments at the following time-points: 0 hours (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, 36, 48 and 72 hours post-dose.
PK Data Analysis: C _{max} , C _{min} , AUC (0-t) and AUC (0-∞), K _e and T _{1/2} were calculated for all treatments.
Analytical Methods: HPLC with UV detection

Statistical Analysis: ANOVA was performed. The 90% CI of the fed group means relative to the fasted group means for natural log transformed Cmax, AUC (0-t) and AUC (0-inf) was obtained. No food effect would be concluded if the 90% CI were contained within the interval of 80 % to 125 %. Gender effect was also examined for natural log transformed Cmax, AUC (0-t) and AUC (0-inf). Tmax was examined using a Wilcoxon's signed rank test.

Results:

Demographics:

Parameter/Statistic	N = 30
Age (years) [Mean ± SD]	27 ± 6.8
Range	[18-44]
Gender: Male / Female	16 men and 14 women
Ethnic Origin	
Black	5
Caucasian	22
Asian	1
Hispanic	1
Hispanic/Korean	1
Height (cm) [Mean ± SD]	174.9 ± 9.07
Range	[157.5 to 191.5]
Weight (kg) [Mean ± SD]	74.1 ± 10.25
Range	[55 to 92]

Pharmacokinetics

Plasma Concentration VS. Time data:

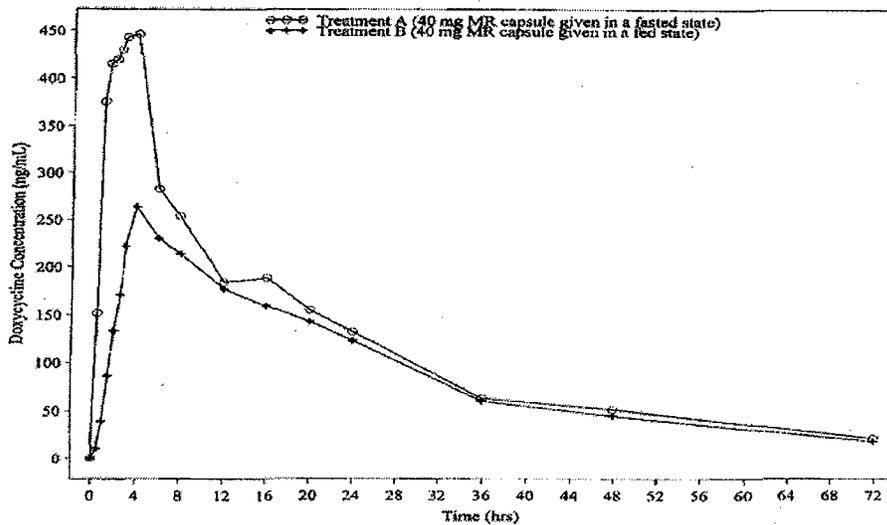


Figure 14.2.1-1 Mean Plasma Doxycycline Concentration versus Time Profile in the Normal Scale

Pharmacokinetic Parameters:

Table 11.b Summary Table of Pharmacokinetic Parameters for Doxycycline

Day	Mean PK Parameters ^a	Units	Treatment ^b	
			A	B
1	C _{max}	(ng/mL)	510 (220.7)	280 (98.2)
	t _{max}	(hr)	3.00 (1.00, 4.12)	4.00 (2.50, 16.0)
	AUC ₀₋₁	(ng·hr/mL)	8189 (2999.1)	6419 (2282.9)
	AUC _{0-∞}	(ng·hr/mL)	9227 (3212.8)	7298 (2459.3)
	t _{1/2}	(hr)	21.2 (7.64)	23.5 (9.16)

Source: Tables 14.2.2.1 and 14.2.2.2

Applicant's Summary

Doxycycline was readily absorbed after both Treatments A and B with median t_{max} of 3 and 4 hours, respectively. After reaching C_{max}, the plasma concentrations of doxycycline slowly declined with an arithmetic mean t_{1/2} of 21.2 (± 7.64) hours for TX A and 23.5 (± 9.16) hours for TX B. There was no marked difference in t_{1/2} between the two treatments.

Following Treatment A (fasted), doxycycline had higher arithmetic mean C_{max} and AUC values relative to Treatment B (fed state) indicating a food effect.

Reviewer's Comments: Following TXB, T_{max} was highly variable compared to that of TXA.

Statistical Comparison of Pharmacokinetic Parameters:

]

Table 11.c Summary Table of Statistical Results of the Rate and Extent of Absorption of Doxycycline

Statistical Analysis of Pharmacokinetic Data:
Treatment B Relative to Treatment A

Parameter	Units	Test Least Squares Mean (Treatment B)	Reference Least Squares Mean (Treatment A)	Test/Reference	90% Confidence Interval	Treatment P-value
C _{max}	ng/mL	266	470	56.6	(51.53, 62.06)	NA
AUC ₀₋₁	ng·hr/mL	6091	7713	79.0	(73.46, 84.90)	NA
AUC _{0-∞}	ng·hr/mL	6954	8730	79.7	(74.27, 85.45)	NA
K _e	1/hr	0.0334	0.0359	93.2	(81.47, 104.95)	NA
t _{max}	hr	4.00	3.00	NA	NA	<0.0001

Source: Table 14.2.3-1.

Applicant's Overall Conclusion:

The rate and extent of doxycycline absorption after a single dose were lower for Treatment B (fed) in comparison to treatment A (fasted). The 90% confidence intervals for ln (C_{max}), ln (AUC_{0-t}), and ln (AUC_{0-∞}) were outside the interval 80% to 125%, indicating that the two treatments were dissimilar.

Gender Effect: Doxycycline pharmacokinetics was compared in 16 men and 14 women under fed and fasted conditions. A significant (p < 0.05) gender effect was observed on the rate and extent of doxycycline absorption. Further, for the rate (C_{max}) of doxycycline absorption, a significant (p < 0.05) gender effect was observed between treatments. These results are consistent with historical (e.g. Periostat Tablets) doxycycline PK data.

Summary of PK Parameters for Doxycycline: Gender Effect

Gender	Mean PK	Gender
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Study Center (s)	
Objectives: To compare Test treatment (Treatment A: 75/25 IR/DR capsule) to the reference treatment (Treatment B: Periostat® administered BID) to determine the rate (Cmax) and extent of absorption (AUC 0-t and AUC 0-∞) of doxycycline	
Study Population Demographics: 18 healthy male and female subjects entered and 17 completed the study	
Study Design: Open-Label, Randomized, 3-way Crossover, Single-Center Study	
Study Period: 04 April 2003 to 01 July 2003	
Investigational Product (s): Periostat-extended-release capsules (75/25 IR/DR capsules containing 40 mg doxycycline monohydrate), Lot # B03003 and Periostat® tablets containing 23 mg doxycycline hyclate (equivalent to 20 mg of doxycycline), Lot # B02174A manufactured by	
Drug Administration: Subjects were randomly assigned to one of 6 possible sequences (i.e. I: ABC, II: BCA, III: CAB, IV: ACB, V: BAC, VI: CBA). Treatment A was a single 40-mg 75/25 mg IR/DR capsule. Treatment B was one 20-mg Periostat tablet and Treatment C was two 20-mg tablets of Periostat tablets. Each dose was administered with 180 mLs of water. Morning doses were administered after at least an 8 hour overnight fast and 12 hour doses were administered after a 2 hour fast. All doses were followed by at least a 4-hour fast from food. Wash out period was 7 days between treatments.	
PK Sampling Scheme: 7 mLs of blood samples were collected on Day 1 for both treatments at the following time-points: 0 hours (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 12 (prior to evening dose, if applicable), 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 20, 24, 36, 48 and 72 hours post-dose.	
PK Data Analysis: Cmax, AUC (0-24), AUC (0-t) and AUC (0-inf), Ke and T _{1/2} were calculated for all treatments.	
Analytical Methods: HPLC with UV detection	
Statistical Analysis: BA was assessed by examining the point estimates of the ratio of each test group mean relative to the reference group mean. ANOVA was performed. The 90% CI of the TX A relative to TX B and C means for natural log transformed Cmax, AUC (0-t) and AUC (0-inf) was obtained for informational purposes only. Exploratory analyses of TXB versus TXC were also performed. Tmax was examined using a Wilcoxon's signed rank test.	
Results:	
Demographics:	
Parameter/Statistic	N = 18
Age (years) [Mean ± SD]	33 ± 7.8
Range	[22-45]
Gender: Male / Female	9 men and 9 women
Ethnic Origin	
Black	2
Caucasian	16
Height (cm) [Mean ± SD]	173.4 ± 6.82
Range	[163.0 to 189.5]
Weight (kg) [Mean ± SD]	72.4 ± 8.29
Range	[57.8 to 89.5]
<i>Subject 8 was discontinued due to a positive alcohol screen. He only received the first treatment (Treatment C in Period 1).</i>	
Pharmacokinetics	
<u>Plasma Concentration vs. Time data:</u>	

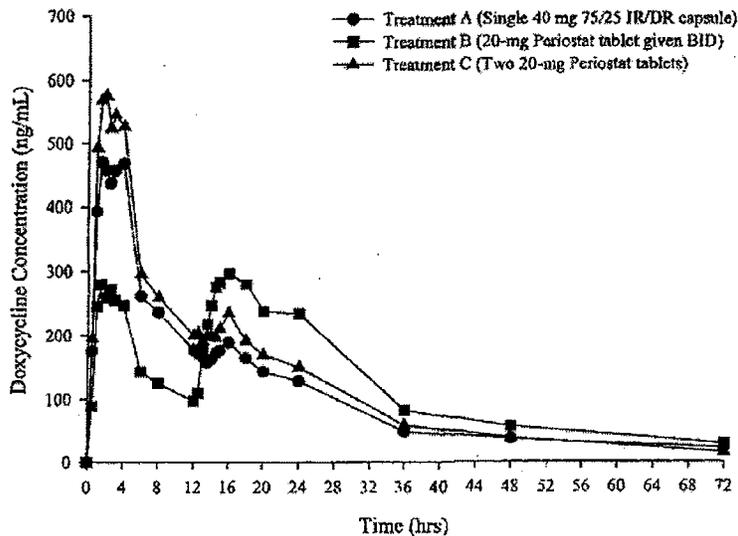


Figure 14.2.1-1. Mean Plasma Doxycycline Concentration versus Time Profile in the Normal Scale.

Pharmacokinetic Parameters:

Table 11.4.1.1-1: Summary Table of Pharmacokinetic Parameters

Treatment ^a		PK Parameters					
		C _{max} (ng/mL)	t _{max} ^b (hr)	AUC ₀₋₂₄ (ng·hr/mL)	AUC ₀₋₁ (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (hr)
A	MEAN	523	2.00	5497	7323	7962	15.1
	SD	204.0	(1.00, 4.00)	1921.9	2495.8	2721.6	5.49
B	MEAN	363	13.5	4931	8321	9229	16.0
	SD	185.7	(1.00, 18.0)	1876.9	3553.6	3877.6	4.66
C	MEAN	623	1.50	6373	8745	9570	20.8
	SD	245.9	(1.00, 4.00)	2476.0	3789.2	4050.7	14.52

Note: Results excerpted from Tables 14.2.2.1, 14.2.2.2, and 14.2.2.3

Reviewer's Comments: Applicant stated that the relatively high median T_{max} value for treatment B could be attributed to the T_{max} occurring during the PM dose of the 12-hour BID dosing regimen. Treatment C had the highest value for mean C_{max} and AUC_{inf} in comparison to Treatments A and B. Treatment A had a higher C_{max}, but lower AUC_{inf} than treatment B. Mean t_{1/2} values were similar across treatments.

Statistical Comparison of Pharmacokinetic Parameters

Table 11.4.1.2-1: Summary Table of Statistical Results of Relative Bioavailability of Doxycycline

Comparison of Treatments	Parameter	Test Mean ^a	Reference		90% Confidence Interval ^c
			Mean ^a	Test/Reference ^b	
A to B	ln(C _{max})	481	328	147	(125, 172)
	ln(AUC ₀₋₂₄)	5175	4622	112	(97.7, 128)
	ln(AUC _{0-t})	6965	7735	90.0	(76.2, 106)
	ln(AUC _{0-∞})	7567	8592	88.1	(75.7, 102)
A to C	ln(C _{max})	481	545	88.2	(75.3, 103)
	ln(AUC ₀₋₂₄)	5175	5678	91.1	(79.6, 104)
	ln(AUC _{0-t})	6965	7620	91.4	(77.3, 108)
	ln(AUC _{0-∞})	7567	8441	89.6	(77.0, 104)
C to B	ln(C _{max})	545	328	166	(142, 195)
	ln(AUC ₀₋₂₄)	5678	4622	123	(107, 141)
	ln(AUC _{0-t})	7620	7735	98.5	(83.4, 116)
	ln(AUC _{0-∞})	8441	8592	98.2	(84.4, 114)

Note: Results are presented from Table 11.4.1.2.1

Reviewer's Comments:

TX A to B Comparison: C_{max} was significantly higher for Treatment A in comparison to Treatment B and the 90% CI was outside the 80-125 % range. Mean AUC inf and AUC (0-t) values for TX A were lower than that of TX B while Mean AUC 0-24 or TXA was higher than that of TX B. This was also reflected in the 90 % CI obtained being outside the 80-125 5 range. Therefore, TX A did not have a similar rate and extent of absorption to TX B. Exploratory comparisons of TX A to C: Indicated that the rate and extent of both treatments were dissimilar. Doxycycline had a lower rate and extent of absorption from TX A compared to TX C. Exploratory comparisons of TX C to B: Indicated that the rate and extent of both treatments were dissimilar. Doxycycline had higher rate and extent of absorption from TX C compared to TX B. However, this was not consistent for the extent of absorption because the AUC (0-t) and inf were similar between the two treatments in that the 90% CI were within 80 to 125 %.

Applicant's Overall Conclusion: *The 75/25 IR/DR capsule had a higher C_{max} but comparable AUC 0-inf for doxycycline relative to the BID Periostat ® treatment. Exploratory comparisons indicate that treatments A and C are comparable with respect to doxycycline bioavailability. The AUC0-t and AUC inf ratio comparison of Treatment A versus Treatment C suggests that the modified-release formulation was approximately 91 % absorbed. Treatment C has a higher C_{max} but comparable AUCinf for doxycycline relative to Treatment B.*

Reviewer's Comments: Applicant's conclusions on comparability are based on numerical values and not on 90% CI.

Analytical Method validation

Compound	Doxycycline
Internal Standard	
Matrix	Plasma
Accuracy (DMT%) <i>Between-Day</i>	-1.0 to 10.7
Precision (CV %) <i>Between-Day</i>	7.6 to 14.2 %
Standard curve range	15 to 500 ng/mL (r = 0.997, n = 23)
Sensitivity (LOQ)	15 ng/mL (% CV = 6.0, n = 22)

Selectivity	No interfering peaks were observed at the retention times of interest.
Stability	Applicant stated that sample stability was previously established and shown to be stable when stored @ ~ s-20°C. Raw data was not included in the submission so I could not confirm this statement.
Conclusions	Is Method Acceptable? Applicant stated and showed that a large number of samples yielded concentration levels that were above the range of the calibration curve. These samples were reassayed, however, diluting to bring them within the range of the standard curve could have introduced another source of error. Basically method was not validated for the concentration range of interest. The concentration range over which the analyte will be determined was not well-defined in the bioanalytical method, however, The ability to dilute samples originally above the upper limit of the standard curve was demonstrated by accuracy and precision parameters in the validation.
DMT = Deviation of mean from theoretical	
Labeling Claims from Study: None	

Study Number: PERIO-DOXYSR-104

Title of Study: An Open-Label, Randomized, Two-Treatment, Two-Way Crossover, Pharmacokinetic Study to Compare an Extended-Release Doxycycline Capsule (40 mg) Administered Orally Once Daily (QD) For Seven Days Versus Periostat® Tablets (20 mg) Administered Orally Twice Daily Twelve Hours Apart (BID) For Seven Days in Normal, Healthy Male and Female Volunteers
Principal Investigator (s): _____
Study Center (s): _____
Objectives: To compare the pharmacokinetics of the test treatment (Treatment A: 75/25 IR/DR capsule administered orally QD) with that of the reference treatment (Treatment B: Periostat ® administered orally BID).
Study Population Demographics: 14 healthy male and female subjects entered and 13 completed the study
Study Design: Open-Label, Randomized, 2-way Crossover, Single-Center Study
Study Period: 14 July 2003 to 29 September 2003
Investigational Product (s): Periostat-extended-release capsules (75/25 IR/DR capsules containing 40 mg doxycycline monohydrate), Lot # B03003 and Periostat® tablets containing 23 mg doxycycline hyclate (equivalent to 20 mg of doxycycline), Lot # B02401A manufactured by _____
Drug Administration: Treatment A: On each of 7 consecutive days, a single 40-mg 75/25 IR/DR capsule was administered QD. Treatment B: On each of six consecutive days, one 20-mg tablet of Periostat was administered BID (12 hours apart). On the seventh day, one 20-mg tablet of Periostat was administered in the morning. Each dose was administered with 180 mLs of water. All subjects were fasted for 7 hours before every AM dose, for 4 hours after every AM dose, and from 2 hours before through 4 hours after the PM dose (TX B) or the PM time-point (TX A) All doses were followed by at least a 4-hour fast from food. Wash out period was 96 hours between the last Period 1 and the first Period 2 PK AM blood collection.
PK Sampling Scheme: 7 mLs of blood samples were collected on Day 1 for both treatments at the following time-points: 0 hours (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 12 (prior to evening dose, if applicable), 12.5, 13, 13.5, 14, 14.5, 15, 16, 18, 20, 24 hours post AM-dose. PK blood draws were also collected for both treatments A and B in both periods at 36, 48 and 72 hours post Study Day 7 AM-dose. Also PK trough blood samples were obtained prior to the AM dose on Nominal Study Days 5 and 6 for both treatments.

PK Data Analysis: On Day 1 and at Steady state (Day 7), C_{max}, AUC (0-24), and T_{max} were calculated. On Day 7, for TX A only, K_e and T_{1/2} were also calculated. For TX B, C_{max} and T_{max} values reported are reflective of data from the AM dose only. Further AUC (0-24) for TX B on Day 7 was approximated, since the PM dose was not administered. The individual subject concentration data for Day 7, TX B, were simulated for time points from 12.5 to 24 hours post AM dose by multiplying the individual concentration data by 0.86 (a factor obtained from food effect studies for Periostat tablets).

Analytical Methods: HPLC with UV detection

Statistical Analysis: BA was assessed by examining the point estimates of the ratio of each test group mean relative to the reference group mean. ANOVA was performed. The 90% CI of TX A relative to TX B means for natural log transformed C_{max} and AUC (0-24) on study days 1 and 7 was obtained. T_{max} was assessed using a Wilcoxon Signed Rank Test. Steady state achievement was assessed by comparing trough plasma concentrations on Nominal Study Days 5, 6, and 7 following administration of TX A or B.

Results:

Demographics:

Parameter/Statistic	N = 14
Age (years) [Mean ± SD]	28 ± 8.3
Range	[19-44]
Gender: Male / Female	7 men and 7 women
Ethnic Origin	
Black	1
Caucasian	10
"mixed"	1
Black and Native American	1
Latino	1
Height (cm) [Mean ± SD]	174.0 ± 8.98
Range	[162.5 to 187.2]
Weight (kg) [Mean ± SD]	70.4 ± 8.78
Range	[56.0 to 91.3]

Subject 9 was withdrawn from the study by the PI for behavioral problems not related to the study treatments. This subject received all Period 1 dosing (TX B) and received Period 2 dosing (TX A from Day 1 through Day 5). This subject's data were not included in PK analyses.

Plasma Concentration VS. Time data:

Reviewer's Comments: Graphs shows that Oracea demonstrates extended release properties, not delayed release.

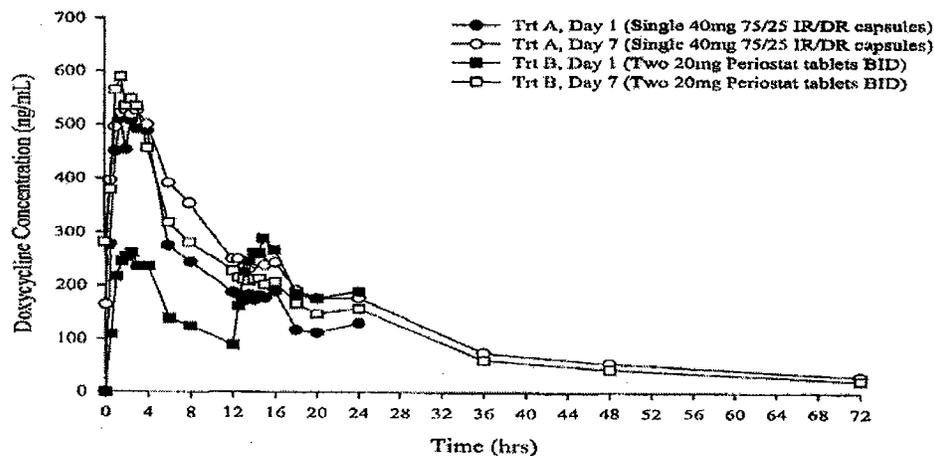


Figure 14.2.1-1. Mean Plasma Doxycycline Concentration versus Time Profile for Days 1 and 7 in the Normal Scale.

Pharmacokinetic Parameters:

Table 11.4.1.2-1: Summary Table of PK Parameters

Day	Mean PK Parameters ^a	Units	Treatment	
			A	B
1	C _{max}	(ng/mL)	586 (159.4)	343 (129.2)
	t _{max} ^a	(hr)	2.50 (1.00, 4.00)	15.0 (0.500, 23.9)
	AUC ₀₋₂₄	(ng·hr/mL)	5588 (1290.5)	4399 (1358.7)
7	C _{max}	(ng/mL)	602 (177.6)	637 (262.2)
	t _{max} ^a	(hr)	2.00 (0.500, 4.00)	1.50 (1.00, 4.00)
	AUC ₀₋₂₄ ^b	(ng·hr/mL)	7230 (1963.9)	8182 (2980.6)

Note: Subject No. 009 data are not included

Applicant's Summary

The results of Table 11.4.1.2. indicates rapid absorption of doxycycline after Treatments A (Oracea 40 mg) with a median t_{max} of approximately 2 hours on both Days 1 and 7. The relatively high median T_{max} value for Treatment B (Periostat BID) on Day 1 could be attributed to the T_{max} occurring during the PM dose of the 12-hour BID dosing regimen. TX A had a higher mean C_{max} and AUC 0-24 value for doxycycline relative to TXB. On Day 7, both treatments had comparable values for C_{max} and AUC 0-24.

Reviewer's Comments: In addition T_{max} for TXA had a lower variability than TXB also. Therefore the absorption was more variable with TXB.

Assessment of SS:

Table 11.4.1.1-1: Trough Concentration (ng/mL) Data for Doxycycline

Treatment	Plasma Concentration (ng/mL)			
	Day 5	Day 6	Day 7	Day 7, 12 hrs
A	187 (120.4)	164 (77.6)	164 (84.5)	NA
B	226 (115.3)	227 (102.1)	282 (149.7)	228 (70.4)

Note: Subject No. 000 data are not included.

Reviewer's Comments: Applicant stated that based on data above, SS for doxycycline was generally achieved by Day 5 for both treatments. In addition the statistical results for the assessment of SS indicated that p-value testing for equality among day arithmetic means was not significant ($P > 0.05$) for treatment A and B, supporting the attainment of SS.

Statistical Comparison of Pharmacokinetic Parameters

Table 11.4.1.3-1: Summary Table of Statistical Results of Relative Bioavailability of Doxycycline

Day	Parameter	Test Mean ^a (Treatment A)	Reference Mean ^a (Treatment B)	Test/Reference ^b	90%
					Confidence Interval ^c
1	ln(C _{max})	564	327	173	(147, 203)
	ln(AUC ₀₋₂₄)	5446	4248	128	(114, 144)
7	ln(C _{max})	578	596	97.0	(86.0, 109)
	ln(AUC ₀₋₂₄)	6991	7744	90.3	(82.2, 99.2)

Note: Subject No. 000 data are not included.

Reviewer's Comments: On Day 1, 90% CI for ln C_{max} and lnAUC were outside the 80-125 % range indicating that both treatments were dissimilar. On Day 7, 90% CI for ln C_{max} and lnAUC were within the 80-125 % range indicating that both treatments were equivalent. However, this should be interpreted with caution since the AUC 0-24 for TX B on Day 7 was estimated.

Applicant's Overall Conclusion:

Doxycycline C_{max} and AUC₀₋₂₄ were significantly higher for Treatment A in comparison to Treatment B on Day 1. On Day 7, the two treatments were bioequivalent as measured by C_{max} and AUC 0-24 for doxycycline. Due to the PM dose not being administered on Day 7, the PK parameter for treatment B on Day 7 were approximated, based on the achievement of steady state, and on the use of previously published food effect data for Periostat. The Day 7 comparison for these results from this pilot study need to be confirmed in a definitive study that will incorporate PM dose administration on Day 7 for Treatment B.

Analytical Method validation

Compound	Doxycycline
Internal Standard	
Matrix	
Accuracy (DMT%) Between-Day	-4.0 to -1.3
Precision (CV %) Between-Day	5.9 to 9.1
Standard curve range	15 to 1200 ng/mL (r=0.9988 n=29)
Sensitivity (LOQ)	15 ng/mL (% CV =7.8, n=24)
Selectivity	No interfering peaks were observed at the retention times of interest.

Stability	Applicant stated that long term stability was in progress
Conclusions	Is Method Acceptable? <i>Applicant stated majority of the samples were re-assayed due to an instrument problem.</i>

DMT = Deviation of mean from theoretical

Labeling Claims: None

Study Number: 110801 (Report summary is provided here. The applicant stated that the full study report was submitted to NDA 50,783 on April 1, 2003, this was however not reviewed because I cannot find the review in DFS). Brief synopsis is provided here since the product used in this study is different from the to-be-marketed formulation

Title of Study: An Evaluation of the Oral Bioavailability of Doxycycline Hyclate Directly Released in the Stomach, Early Small Intestine, Distal Small Intestine and Colon Using Gamma Scintigraphy and the Capsule

Principal Investigator (s): Not Specified

Study Center (s): Not Specified

Objectives: 1) To compare the relative bioavailability of doxycycline (20 mg) following site-specific drug release via an _____ o the early small intestine, distal small intestine, and cecum/colon, as compared to doxycycline absorption when delivered orally in an immediate release capsule, 2) correlate the pharmacokinetic (drug levels) and scintigraphic data (GI transit) and 3) from these results determine the viability of a sustained release formulation for doxycycline

Study Population Demographics: 8 healthy male volunteers

Study Design: Open-label, four-period, four treatment crossover study

Study Period: Not Specified

Investigational Product (s): Doxycycline 20 mg (as 23.2 mg of doxycycline hyclate) in an immediate release hard gelatin capsule, No. 2, radiolabeled with Indium-111chloride (Reference) and, Doxycycline powder radiolabeled with Indium-111 chloride and administered via an _____ capsule

Drug Administration: Subjects received the following treatments in a randomized order: Single 20 mg dose of doxycycline in an immediate release capsule, radiolabeled with Indium-111chloride (TX A), Single 20 mg dose of doxycycline powder, radiolabeled with Indium-111chloride and administered via an _____ capsule to the early intestine (TX B), Single 20 mg dose of doxycycline powder, radiolabeled with Indium-111chloride and administered via an _____ capsule to the distal small intestine (TX C) and Single 20 mg dose of doxycycline powder, radiolabeled with Indium-111chloride and administered via an _____ capsule to the cecum/colon (TX D).

Subjects fasted overnight before drug administration and food was not permitted until at least 4 hr post-dose. The remote control capsules were administered with 240 mLs of water containing technetium-99m DTPA ($t_{1/2} = 6.0$ hrs, $\gamma = 140$ keV) to help delineate the gastrointestinal tract when targeting specific regions with the _____ capsule. The control treatment (TX A) was only radiolabeled with Indium-111 and a total volume of 240 mL of non-radioactive water was also ingested with the control treatment.

Immediately after ingestion of the radiolabeled capsule, subjects were positioned supine beneath the scintillation camera. Subjects were imaged continuously for approximately three minutes at 15 to 30 minute intervals until it was confirmed that the capsule had reached the intended gastrointestinal site of study. The remote control capsule is then externally activated and imaging then coincides with blood sampling times. Data were acquired in 1 minute increments and stored on a computer generating a time-activity study.

PK Sampling Scheme: Blood samples were collected from a venous catheter into a vacuum tube (2 mL EDTA as anti-coagulant) at pre-dose, just prior to capsule activation (0hr), and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, and 24 hours post drug release (or after capsule activation)

Analytical Methods: Applicant stated that plasma concentrations were determined by a validated analytical method

Scintigraphic Analysis: The sequential computer generated images were reviewed for each subject and regions of interest (ROI) were drawn to represent the stomach, early small intestine (approximately jejunum), distal small intestine (approximately ileum) and cecum/colon. All counts were background corrected and also corrected for radioactive decay. Dynamic gastrointestinal transit plots were generated which depicted the relative percent of radioactivity in each region of interest versus time, and the plasma concentration profile of doxycycline was then overlaid on these GI transit curves.

PK data Analysis: Applicant stated that the resulting concentration-time data were subjected to non-compartmental pharmacokinetic analysis.

Results:

Applicant's Summary

- The relative bioavailability of doxycycline compared to the control treatment (administration of 20 mg of doxycycline via an immediate release gelatin capsule) was $89.2 \pm 7.6 \%$, $37.4 \pm 19.2 \%$ and $4.5 \pm .4 \%$ for delivery to the early small intestine, distal small intestine and colon, respectively. The relative bioavailability ranged from a) 80.6 to 104.9 %, for the early small intestine, b) 6.5 % to 51.5 % for the distal small intestine and c) 0.3 to 17.1 % for the colon.
- Once doxycycline was released from the capsule, the initiation of drug absorption typically started by the first blood sampling time (0.25 hrs). However, T_{max} was usually reached later which suggested that absorption of doxycycline was likely to be rate limited due to either a decreased permeability or stability of the drug in the distal regions of the small intestine and colon.
- The data described in this report collectively indicate that the extent of doxycycline absorption decreased as the drug was released further down the gastrointestinal tract.

Applicant's Conclusions:

- The lower plasma AUCs following release in the distal small intestine and colon were most likely attributed to a reduction in the overall permeability or chemical stability of the released drug in those regions of the gastrointestinal tract.
- It has been our experience that the reduction of absorption of soluble drugs like doxycycline are commonly influenced by a regional residence time and/or the small intestine transit time. However, in this study, the residence time of the drug was found not to be correlated with the extent of absorption of doxycycline in the different regions of the gastrointestinal tract. Thus, the reduction of the extent of absorption as a function of the delivery of the drug more distally down the small intestine was attributed to a decrease in permeability or chemical stability in the three segments of the GI tract (early small intestine > distal small intestine > colon).
- The results indicate that in order to have a chance of achieving a viable sustained release dosage form for doxycycline, the knowledge of why the permeability decreases distally in the gastrointestinal tract must be explored. This reduction may be due to the presence of more solid particulate being present in the terminal small intestine and colon where the drug binds to these particles and thus reduces the amount available for absorption. It may also possibly be due to a change in regional environment (pH, bacterial resistance, metal ion concentration, etc.) which effects the absorption characteristics of the drug. Doxycycline may also benefit by increasing its apparent absorption window. If it is possible to increase either drug permeability via the use of absorption enhancers (and therefore increase the extent of absorption) or drug stability with different ion pairing, then it follows that it will become easier to achieve a sustained absorption profile.

Reviewer's Comments: Basically this pilot study showed that doxycycline was absorbed mainly in the upper part of the gastrointestinal tract (Scintipharma study report submitted to NDA 50-783 on April 1, 2003). These findings were helpful in defining the final DR bead formulation.

Labeling Claims from Study: Gastric Insufficiency:

Literature Reference: Grahn et al, 1994

Objective:

The applicant included a published report by Grahn et al (1994) that evaluated the effect of increased gastric pH (obtained by pre-treatment with omeprazole) on the bioavailability of doxycycline monohydrate and doxycycline in 24 healthy volunteers, using an open, randomized, four-treatment, four-period, crossover, 2 x 2 factorial design. Each subject received a single dose of 100 mg of each of the doxycycline formulations with and without pre-treatment with omeprazole (40 mg daily for 7 days).

Results:

The two formulations were found to have a comparable rate and extent of absorption during fasting without omeprazole pre-treatment. After omeprazole, the monohydrate showed a highly significant decrease in bioavailability (38% for AUC and 45% for C_{max}) compared to the carrageenate formulation, which was not affected by prior administration of omeprazole. Many of the subjects did not reach a therapeutic plasma level of doxycycline during the combination of omeprazole and doxycycline monohydrate, and most adverse events (mainly gastrointestinal) were reported after this combination. PK data are inserted below as Table 1, 2 and 3.

Table 1. Single dose pharmacokinetic parameters of doxycycline in subjects without omeprazole pre-treatment. Mean (SD)

Parameter	Formulation	
	Doxycycline carrageenate	Doxycycline monohydrate
AUC ₍₀₋₄₎ [$\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$]	23.4 (5.50)	26.8 (5.33)
AUC _(0-∞) [$\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$]	26.8 (7.03)	29.9 (5.83)
C _{max} [$\mu\text{g}\cdot\text{ml}^{-1}$]	1.54 (0.40)	1.75 (0.45)
t _{max} [h]	2.0 (1.0)	2.0 (0.9)
λ [$1\cdot\text{h}^{-1}$]	0.0483 (0.0084)	0.0506 (0.0087)
t _{1/2, z} [h]	14.8 (2.6)	14.1 (3.4)
MRT [h]	21.8 (4.2)	20.8 (3.4)

Table 2. Single dose pharmacokinetic parameters of doxycycline in subjects pretreated with omeprazole. Mean (SD)

Parameter	Formulation	
	Doxycycline carrageenate	Doxycycline monohydrate
AUC ₍₀₋₄₎ [$\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$]	21.8 (5.56)	13.6 (4.63)
AUC _(0-∞) [$\mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$]	24.5 (6.44)	16.0 (5.42)
C _{max} [$\mu\text{g}\cdot\text{ml}^{-1}$]	1.31 (0.34)	0.77 (0.31)
t _{max} [h]	2.1 (1.1)	2.7 (1.1)
λ [$1\cdot\text{h}^{-1}$]	0.0481 (0.0086)	0.0428 (0.0088)
t _{1/2, z} [h]	14.9 (2.8)	14.1 (2.3)
MRT [h]	21.0 (4.5)	23.8 (5.8)

Table 3. Mean treatment ratios (%), 90% confidence intervals (within parentheses) and corresponding P-values on comparing the different treatments

Parameter	A1/A2		A1/A2	
	Without omeprazole	P	With omeprazole	P
AUC _(0-∞)	88 (77-100)	0.1059	162 (141-186)	0.0001
C _{max}	88 (77-100)	0.0927	182 (160-207)	0.0001
λ	96 (90-101)	0.1967	113 (107-119)	0.0012

A1, Doxycycline carrageenate; A2, doxycycline monohydrate

Dissolution Method Development Report (Technical Report #. TR-02-22)

Protocol VP-03-010 "Dissolution Procedure for SL1444 Capsules (Method Development)":

Proposed Dissolution Method:

Apparatus	USP Dissolution Apparatus II (Paddles)
Media	
Sampling Time Points	
Agitation Speed	
Temperature	
Specifications	

Dissolution Method Development: (formulation used lot # B03003, composed of a ratio of 3:1 IR ~ DR — used in PK study 103 and 104)

The objective of this study was to evaluate the optimal dissolution parameters for the final SL1444 formulation, to support Phase III clinical and NDA stability batches. The selected formulation was tested under various conditions _____ for agitation speed. In addition, sink conditions were also studied by obtaining the dissolution profile for three 40 mg capsules corresponding to 120 mg.

Agitation Study: Paddle rotation speeds of _____ were evaluated on the media described in the dissolution method using Oracea 40 mg capsules. Three dissolutions were performed at the _____ agitation speed because the first result obtained was considered unexpected due to the low % dissolved at _____ ur time point, and the low recovery at the _____ hour time point. Inserted below is dissolution data for ' _____ (Investigation # 3)

Table 6. Dissolution Data for _____

	
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2 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

4.4 OCPB Filing Form:

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
<i>General Information About the Submission</i>			
	Information		Information
NDA Number	50-805	Brand Name	Oracea
OCPB Division (I, II, III)	DPEIII	Generic Name	Doxycycline
Medical Division	HFD-540	Drug Class	Antibiotic
OCPB Reviewer	Abi Adebowale	Indication(s)	inflammatory lesions in patients with rosacea
OCPB Team Leader	Dennis Bashaw	Dosage Form/Strength	Capsules 40 mg
		Dosing Regimen	Once daily in the morning. If it is taken close to meal times, it is recommended that it be taken at least one hour prior to or two hours after meals.
Date of Submission, Filing Date	August 1st, 2005 September 30th, 2005	Route of Administration	Oral
Mid Cycle Review Date	Not Yet decided	Type of Submission	Original NDA
Estimated Due Date of OCPB Review	March 1st, 2006	Sponsor	Collagenex Pharmaceuticals, PA
PDUFA Due Date	June 1st, 2006	Priority Classification	3S

Division Due Date	March 15th, 2006	IND Number (s)	67,833 and
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Clin. Pharm. and Biopharm. Information

Background and Introduction: Collagenex Pharmaceuticals, Inc. had previously developed the approved drug Periostat® (doxycycline hyclate tablets) 20 mg (NDA 50-783) for use twice daily as an adjunct to scaling and root planning to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis. Preliminary studies that suggested efficacy and safety of doxycycline at subantimicrobial doses for treating rosacea, as well as an understanding of the possible mechanism of action of subantimicrobial doses for this indication, led the sponsor to develop a controlled-release oral formulation to allow patients to take the product once daily. The Oracea® formulation was designed to provide an extended release profile in vivo of doxycycline concentrations that at steady state are high enough to have a beneficial effect but not high enough to exert an antibacterial effect. The goal of Oracea® formulation development was a product suitable for once-daily administration that was bioequivalent to Periostat® in terms of area under the concentration-time curve (AUC) while maintaining the maximum plasma level (Cmax) so as not to exceed the antimicrobial threshold of 1.0 mcg/mL. Oracea® contains two types of beads that together provide a dose of 40 mg of doxycycline. The immediate release (IR) beads contain 30 mg of doxycycline and the delayed-release beads contain 10 mg.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1		COL-101-SSPK-106
Patients-				
single dose:				
multiple dose:		1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD (HEALTHY OR PATIENTS):				
Phase 1 or 2:				

Phase 3:				
PK/PD (HEALTHY OR PATIENTS):				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability (oral BA):	X			110801 (oral BA of doxycycline hyclate using gamma scintigraphy and the capsule) This study may not be relevant (not TBMF, and different salt)
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			PERIO-DOXYSR-103 and 104 (formulation used not TBMF.) Study only supportive
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			COL-101-SDPK-105
Dissolution:	X			Confirm with the review chemist that the sponsor included data on method development using clinical lots in the NDA. Only found specifications in my volumes
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				
Literature References			1	
Total Number of Studies			4 and 2 study summaries	
Fileability and QBR comments				
	"X" if yes	Comments		
		Applicant provided dissolution method and specifications but no data in Module 2 Vol 1.1. Asked the chemistry reviewer if applicant provided dissolution data using clinical/BA batches in the chemistry section (he will get back to me). Also Chemist is going to make sure that the drug product used to conduct the clinical trials was the same as the TBMF (to be marketed formulation).		
Application fileable?	X	Reasons if the application is <u>not</u> fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?	NA	Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)		<p><i>Does the drug product meet the controlled release claims made for it?</i></p> <p><i>Does the BA profile of the drug product rule out the occurrence of dose dumping?</i></p> <p><i>Is the drug product's steady state performance comparable/equivalent to that of a currently marketed RLD?</i></p> <p><i>Is there a food-effect on the highest strength of the drug product?</i></p> <p><i>Do we need a PM consult? No</i></p>		

Other comments or information not included above	
Primary Reviewer Signature and Date	Abi Adebawale (09/08/2005)
Secondary reviewer Signature and Date	

CC: NDA 21-789, HFD-850 (P.Lee), HFD-540 (M .Kozma-Fornaro), HFD-880 (D. Bashaw, A. Selen)

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- viii. Saivain S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinetics.* 1988; 15:355-366
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/s/

Abi Adebawale
5/16/2006 11:01:27 AM
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Dennis Bashaw
5/17/2006 04:41:50 PM
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