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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-783

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology/Biopharmaceutics Review

Submission:	NDA 50-783
Product Trade Name:	Periostat [®] (Doxycycline hyclate, 20 mg)
Dosage Form:	Tablet
Indication:	Periodontal Disease
Submission Date:	April 3, 2000
Type of Submission:	Original NDA (3S)
Sponsor:	CollaGenex Pharmaceuticals, Inc.
Reviewer:	Tapash K. Ghosh, Ph.D.
Team Leader:	Dennis Bashaw, Pharm. D.

Background: The current clinical study was designed to test the bioequivalence of two different formulations of doxycycline hyclate--the currently-marketed 20 mg capsule versus a 20 mg tablet. In addition, the study was designed to determine if ingestion of a high-fat, high-calorie meal immediately before the administration of a single 20-mg oral dose of doxycycline hyclate would alter the absorption of doxycycline in healthy adult subjects.

Synopsis: Doxycycline is a member of the tetracycline family of antibiotics. It has been shown to be effective at sub-antimicrobial dosages in reducing elevated levels of collagenase associated with adult periodontitis. Evidence from dose-response studies has shown that doxycycline, at a dose of 20 mg b.i.d., is effective in reducing excessive gingival crevicular fluid collagenase activity in subjects with periodontitis. The purpose of this study was two-fold: to test for bioequivalence between the currently-marketed doxycycline hyclate 20 mg capsule and a doxycycline hyclate 20 mg tablet; and to evaluate possible food effects in the pharmacokinetic profile of doxycycline hyclate 20 mg tablets. This was a randomized, single-dose, three-treatment, three-period, six-sequence crossover study. The absorption and distribution of doxycycline was determined in healthy adult subjects, age 18 to 40. Per the protocol, a minimum of 18 subjects (nine males and nine females) was to be enrolled. However, twenty subjects (nine males and eleven females) actually entered the study. It was found that the capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. Food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

Recommendation: Based on the review, NDA 50-783 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A review of the PK data in this submission resulted in certain changes that are included in the "Labeling Comments" and have been conveyed to the reviewing division.

Tapash K. Ghosh, Ph.D.
OCPB, DPE III

Dated _____

Team Leader: E. Dennis Bashaw, Pharm.D.

Dated _____

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A RANDOMIZED, SINGLE-DOSE, THREE-TREATMENT, THREE-PERIOD, SIX-SEQUENCE CROSSOVER STUDY TO ASSESS THE EFFECTS OF FOOD ON THE PHARMACOKINETICS OF PERIOSTAT® (DOXYCYCLINE HYCLATE) 20 MG TABLETS AND TO ASSESS THE BIOEQUIVALENCE OF DOXYCYCLINE HYCLATE 20 MG CAPSULES COMPARED TO DOXYCYCLINE HYCLATE 20 MG TABLETS

1. INTRODUCTION

Doxycycline is a member of the tetracycline family of antibiotics. It has been shown to be effective at sub-antimicrobial dosages in reducing elevated levels of collagenase associated with adult periodontitis. Evidence from dose-response studies has shown that doxycycline, at a dose of 20 mg b.i.d., is effective in reducing excessive gingival crevicular fluid collagenase activity in subjects with periodontitis. Side effects related to sub-antimicrobial administration of doxycycline are similar to placebo.

The current clinical study was designed to test the bioequivalence of two different formulations of doxycycline hyclate--the currently marketed 20-mg capsule versus a 20-mg tablet. In addition, the study was designed to determine if ingestion of a high-fat, high-calorie meal immediately before the administration of a single 20-mg oral dose of doxycycline hyclate would alter the absorption and distribution of doxycycline in healthy adult subjects. While studies using higher doses of doxycycline hyclate have shown no food effect, no studies had yet been done with a 20-mg b.i.d. dose.

2. STUDY OBJECTIVES

The purpose of this study was two-fold:

- to test for bioequivalence between the currently-marketed doxycycline hyclate 20 mg capsule and a doxycycline hyclate 20 mg tablet; and
- to evaluate possible food effects in the pharmacokinetic profile of doxycycline hyclate 20-mg tablets.

3. STUDY DESIGN

This was a randomized, single-dose, three-treatment, three-period, six-sequence crossover study.

The absorption and distribution of doxycycline was determined in healthy adult subjects, age 18 to 40. Per the protocol, a minimum of 18 subjects (nine males and nine females) was to be enrolled. However, twenty subjects (nine males and eleven females) actually entered the study.

3.1 Treatments

3.1.1 Dosing and Administration of Study Medication

Doxycycline hyclate 20-mg capsules were supplied in bulk to the site by CollaGenex. All capsules were the standard, commercially available formulation of Periostat® (Lot # 99087A).

Doxycycline hyclate 20 mg tablets (Lot # 990205A,B) were supplied in bulk by Pharmaceutical Manufacturing Research Services, Inc. (423 Sargon Way, Horsham, PA 19044)

3.1.2 Method of Assigning Patients to Treatment Groups

Subjects were randomly assigned to receive each of the three treatments in one of the six possible order permutations. The randomization list constrained treatment assignment such that two subjects of one sex and one subject of the opposite sex were assigned to each order permutation.

3.2 Efficacy and Safety Assessments

3.2.1 Study Procedures

The study design required each subject to participate in three separate pharmacokinetic determination procedures:

- Doxycycline hyclate capsule after fasting for 10 hours;
- Doxycycline hyclate tablet after fasting for 10 hours; and
- Doxycycline hyclate tablet after a high-calorie meal.

The procedures began at 7-day intervals and required approximately 82 hours to complete. After a 30-day screening period, subjects were randomized to one of the six possible treatment order permutations. After fasting for 10 hours overnight (no food, only water after 2000 hours until 0500 hours), subjects took the study drug. Subjects assigned to a fasting condition took a single doxycycline hyclate 20 mg dose (tablet or capsule) with 180 mL of water at approximately 0800 hours (\pm 15 minutes). Subjects assigned to the fed condition consumed a FDA recommended breakfast containing approximately 1000 calories, with approximately 50% of the calories being contained in fat. The meal was ingested within a 30-minute period. Dosing with a single doxycycline 20 mg tablet took place within 5 minutes after completion of the meal.

Prior to dosing, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours after dosing, a 7 mL venous blood sample was taken for analysis of plasma concentrations of doxycycline. Subjects underwent a 7-day washout period in between treatment periods.

3.3 Drug Concentration Measurements

Blood samples of approximately 7 mL were taken by venipuncture. Plasma was separated by refrigerated centrifugation (_____). Plasma concentrations of doxycycline base were determined by (_____) following a (_____)
(The method was originally developed and validated by (_____)
(In April 1995. It was later validated by (_____)
(In November 1999 and was used to analyze all the
plasma samples for CollaGenex Pharmaceuticals Inc. Copies of the analysis method description and bioanalysis validation report are included in the submission and considered satisfactory. The summary of the report is described below:

Chromatography Condition:

Column: _____

Detection: _____

Injection volume: _____

Column temperature: _____

Flow rate: _____

Mobile phase: _____

The method involves (_____) followed by (_____)

It is validated for inter- and intra-day accuracy and precision, linearity, and specificity. The method is accurate and precise to an absolute level of 15 ng of doxycycline and is linear up to levels of at least 500 ng. The coefficients of variation ranged from 2.56 to 11.2% for the plasma level range _____ to _____ ng/mL. The accuracy was of the range 94.3 to 112% for this plasma level range.

3.3.1 Pharmacokinetic analysis

The non-compartmental analysis was performed using _____
Doxycycline hyclate was assumed to convert rapidly and completely to doxycycline *in vivo*. Any plasma concentrations below the limit of quantification of the assay (_____ ng/mL) were taken as zero for calculation of descriptive statistics.

C_{max} and time to C_{max} (t_{max}) were determined from the time curves without interpolation. The apparent terminal rate constant (λ_z) was determined by regressing logarithmically transformed concentration on time after excluding the nonlinear portion of the curve.

3.3.2 Evaluation of bioequivalence

Both doxycycline capsule and tablet formulations were administered to subjects after fasting for 10 hours according to the protocol. The primary pharmacokinetic

parameters for the determination of bioequivalence of the tablet formulation to the capsule formulation of doxycycline were:

- the areas under the curve of the plasma concentrations of doxycycline to the last quantifiable concentration (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$); and
- the maximum plasma concentration (C_{max}) of doxycycline.

Secondary pharmacokinetic parameters included:

- time to maximum plasma concentration (t_{max}),
- apparent terminal half-life,
- apparent terminal rate constant,
- ratio of AUC_{0-t} to $AUC_{0-\infty}$, and
- percent of $AUC_{0-\infty}$ obtained by extrapolation.

Descriptive statistics (arithmetic mean, geometric mean, median, minimum, maximum, standard deviation, coefficient of variation, arithmetic mean of logs, standard deviation of logs) were computed for all pharmacokinetic endpoints by treatment and by gender.

Plots of AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} by treatment were generated on a semi-logarithmic scale to provide a visual assessment of the key treatment comparisons.

3.3.3 Evaluation of Food Effect

The primary pharmacokinetic parameters for the comparison of bioavailability (food effect) of the tablet formulation in fed and fasted conditions were the areas under the curve of the plasma concentrations of doxycycline to the last quantifiable concentration (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$), and the maximum plasma concentration (C_{max}) of doxycycline.

3.4 Disposition of Subjects

The disposition of subjects is presented in Table 1.

Table 1. Number of Subjects Receiving Each Possible Treatment Order by Sex

	Treatment Order for ITT Subjects						Total
	FCT	FTC	TCF	TFC	CTF	CFT	
Males	2	0	1	2	1	3	9
Females	1	3	2*	2	2	1	11
Total	3	3	3*	4	3	4	20

F = Fed Tablet; C = Fasted Capsule; T = Fasted Tablet
 *One subject in this cell was excluded from the per-protocol analysis.

4. PHARMACOKINETIC RESULTS AND EVALUATION

4.1 Data Sets Analyzed

Two data sets were analyzed: data from the intent-to-treat population, and data from the per-protocol population. The per-protocol cohort consisted of 19 subjects because all data from Subject 006 (spurious in nature) were excluded from the per-protocol analysis. The intent-to-treat (ITT) cohort consisted of 20 subjects. All the data from these 20 subjects was included in the intent-to-treat analysis, except for the third period data (fed tablet condition) for Subject 006.

4.2 Analyses of Bioequivalence

Summary data for bioequivalence of the doxycycline tablet formulation to the doxycycline capsule formulation are given in Table 2 for both the per-protocol and intent-to-treat populations. Pharmacokinetic parameters of both cohorts for the two formulations taken in the fasted state are presented in Table 3. Individual plasma concentrations for subjects taking each of the two formulations are noted in Table 4. Figures 1 and 2 describes linear and semi-logarithmic plasma concentration-time profiles respectively. Data are presented by gender in Figures 3 and 4.

The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) for per-protocol patients in the fasted capsule condition was 5476 ng.h/mL and for the fasted tablet condition, 5487 ng.h/mL (Table 3). The least squares mean ratio between the two was 99.4%, with the 90% confidence interval falling between 85.6% and 115.4% (Table 2). Similar results were found for AUC_{0-t} . The same conclusions were reached using the ITT population.

The maximum concentration (C_{max}) for per-protocol patients in the fasted capsule condition was 324 ng/mL and for the fasted tablet condition, 347 ng/mL (Table 3). The least squares mean ratio between the two was 106.7, with the 90% confidence interval falling between 95.6% and 119.2% for C_{max} (Table 2). Results for the ITT group were similar to those for the per protocol group.

For per protocol subjects, the mean time to maximum concentration (t_{max}) of doxycycline in plasma was 1.6 hours (range: 1.2 to 2.0 hours) post-dosing in the fasted capsule condition and 1.4 hours (range: 1.0 to 1.8 hours) in the fasted tablet condition (Table 3).

For per protocol subjects, the apparent terminal half-life ($t_{1/2}$) ranged from 15 to 23 hours (with a mean of 19.2 hours) in the fasted capsule condition and ranged from 15 to 21 hours (with a mean of 18.1 hours) in the fasted tablet condition (Table 3).

AUC and C_{max} were higher, and $t_{1/2}$ was shorter in females than males. These gender differences appear to be more marked for the fasted capsule condition compared to the fasted tablet condition (Table 7).

Table 2

Summary of Bioequivalence (BE) Results: Statistics for Treatment Differences and Ratios

Parameter	Variable	N	Per Protocol			Intent-to-Treat			
			Least Squares Mean	90% Lower Confidence Limit	90% Upper Confidence Limit	N	Least Squares Mean	90% Lower Confidence Limit	90% Upper Confidence Limit
AUC 0-inf	T/C	19	99.4%*	85.6%*	115.4%*	20	99.3%	86.1%	114.5%
	T-C		23.1	-887.1	933.3		10.1	-860.6	880.9
AUC 0-t	T/C	19	103.6%*	88.3%*	121.5%*	20	103.0%	88.4%	120.1%
	T-C		194.9	-612.0	1001.9		162.6	-610.4	935.7
Cmax	T/C	19	106.7%*	95.6%*	119.2%*	20	106.4%	95.7%	118.3%
	T-C		19.6	-15.9	55.1		17.9	-16.3	52.0
tmax	T/C**	19	0.25	0.00	0.50	20	0.25	0.00	0.75
	T-C		-0.25	-0.82	0.31		-0.33	-0.87	0.22
t 1/2	T/C	19	94.97%	81.12%	111.18%	20	96.32%	82.73%	112.14%
	T-C		-1.18	-4.39	2.03		-0.96	-4.04	2.11
.mbda_z	T/C	19	105.280%	89.935%	123.242%	20	103.799%	89.161%	120.841%
	T-C		0.002	-0.004	0.008		0.001	-0.005	0.007

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Table 3

Summary of Bioequivalence (BE) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat		
			Males	Females	Total	Males	Females	Total
AUC 0-inf	C	N	9	10	19	9	11	20
		Arithmetic Mean	5111	6356	5766	5111	6390	5814
		Geometric Mean	4925	6025	5476	4925	6086	5533
	Coefficient of Variation (%)	31.0	32.6	33.2	31.0	30.8	32.3	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	5671	5984	5836	5671	5949	5824
Geometric Mean		5259	5700	5487	5259	5691	5493	
Coefficient of Variation (%)	45.6	32.7	38.0	45.6	31.2	37.1		
AUC 0-t	C	N	9	10	19	9	11	20
		Arithmetic Mean	3731	5843	4843	3731	5890	4918
		Geometric Mean	3593	5482	4488	3593	5556	4566
	Coefficient of Variation (%)	30.2	35.5	40.8	30.2	33.6	39.7	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	5069	5089	5079	5069	5091	5081
Geometric Mean		4616	4748	4685	4616	4780	4706	
Coefficient of Variation (%)	50.3	38.3	43.0	50.3	36.3	41.9		
Cmax	C	N	9	10	19	9	11	20
		Arithmetic Mean	247.4	424.4	340.5	247.4	434.6	350.4
		Geometric Mean	243.6	418.1	323.7	243.6	427.7	332.0
	Coefficient of Variation (%)	19.2	16.7	31.9	19.2	17.4	32.6	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	308.3	410.0	361.8	308.3	417.2	368.2
Geometric Mean		294.1	403.2	347.2	294.1	410.4	353.2	
Coefficient of Variation (%)	33.8	18.0	28.0	33.8	17.7	27.9		
tmax	C	N	9	10	19	9	11	20
		Arithmetic Mean	1.61	1.65	1.63	1.61	1.77	1.70
		Geometric Mean	1.46	1.44	1.45	1.46	1.54	1.50
	Coefficient of Variation (%)	57.6	59.0	56.7	57.6	56.9	56.0	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	1.33	1.45	1.39	1.33	1.41	1.38
Geometric Mean		1.27	1.39	1.33	1.27	1.35	1.31	
Coefficient of Variation (%)	37.5	30.2	32.9	37.5	31.0	33.1		
t 1/2	C	N	9	10	19	9	11	20
		Arithmetic Mean	22.02	16.65	19.20	22.02	16.23	18.84
		Geometric Mean	20.94	16.24	18.32	20.94	15.80	17.94
		Coefficient of Variation (%)	37.1	21.8	34.5	37.1	22.9	35.2

Table 3

Summary of Bioequivalence (BE) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat		
			Males	Females	Total	Males	Females	Total
lambda_z	T	N	9	10	19	9	11	20
		Arithmetic Mean	18.70	17.48	18.06	18.70	17.20	17.88
		Geometric Mean	18.18	16.81	17.44	18.18	16.57	17.28
		Coefficient of Variation (%)	25.2	29.5	26.9	25.2	28.9	26.8
	C	N	9	10	19	9	11	20
		Arithmetic Mean	0.0345	0.0440	0.0395	0.0345	0.0452	0.0404
		Geometric Mean	0.0331	0.0427	0.0379	0.0331	0.0439	0.0387
		Coefficient of Variation (%)	27.9	28.8	30.5	27.9	28.1	30.7
	T	N	9	10	19	9	11	20
		Arithmetic Mean	0.0392	0.0429	0.0412	0.0392	0.0434	0.0415
		Geometric Mean	0.0381	0.0412	0.0397	0.0381	0.0418	0.0401
		Coefficient of Variation (%)	25.2	28.9	27.1	25.2	27.4	26.4

Table 4**Plasma Doxycycline Concentrations (ng/mL)****Treatment C**

Patient#	Baseline	<u>Schedule Time Relative to Dosing (hrs)</u>													
		0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	48	72
1.0	<15														
2.0	<15														
3.0	<15														
4.0	<15														
5.0	<15														
6.0	<15														
7.0	<15														
8.0	<15														
9.0	<15														
10.0	<15														
11.0	<15														
12.0	<15														
13.0	<15														
14.0	<15														
15.0	<15														
16.0	<15														
17.0	<15														
18.0	<15														
19.0	<15														
20.0	<15														
Mean	BQL	194.9	286.8	310.6	251.4	262.1	276.0	255.5	170.7	162.8	121.4	115.0	86.4	20.8	7.5
SD	BQL	121.2	112.7	105.9	80.4	81.7	91.9	95.2	66.4	73.9	44.5	52.8	35.6	16.2	10.3
%CV	BQL	62.2	39.3	34.1	32.0	31.2	33.3	37.3	38.9	45.4	36.6	45.9	41.2	78.0	137.3

Table 4 (Contd)

Treatment T			0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	48	72
Patient#	Baseline															
1.0	<15															
2.0	<15															
3.0	<15															
4.0	<15															
5.0	<15															
6.0	<15															
7.0	<15															
8.0	<15															
9.0	<15															
10.0	<15															
11.0	<15															
12.0	<15															
13.0	<15															
14.0	<15															
15.0	<15															
16.0	<15															
17.0	<15															
18.0	<15															
19.0	<15															
20.0	15.4															
Mean	BQL	194.7	311.8	317.6	290.9	281.0	272.4	256.9	172.9	158.6	123.6	102.8	98.1	26.4	8.7	
SD	BQL	115.0	105.8	103.4	82.2	85.2	81.1	78.0	53.6	38.8	34.1	38.5	61.8	20.0	12.4	
%CV	BQL	59.1	33.9	32.6	28.2	30.3	29.8	30.3	31.0	24.5	27.6	37.5	63.0	75.7	141.9	

Treatment F

Patient#	Baseline	0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	48	72
1.0	<15														
2.0	<15														
3.0	<15														
4.0	<15														
5.0	<15														
6.0	661.4														
7.0	<15														
8.0	<15														
9.0	<15														
10.0	<15														
11.0	<15														
12.0	<15														
13.0	<15														
14.0	0.0														
15.0	<15														
16.0	<15														
17.0	<15														
18.0	<15														
19.0	<15														
20.0	<15														
Mean	BQL	23.0	78.5	147.5	168.6	184.9	208.2	245.9	173.4	152.8	126.1	94.5	76.7	25.8	6.7
SD	BQL	36.5	83.0	82.9	60.3	52.5	67.1	82.9	54.0	63.9	39.3	32.2	25.7	17.9	10.7
%CV	BQL	159.1	105.8	56.2	35.8	28.4	32.2	33.7	31.2	41.8	31.2	34.1	33.6	69.5	158.6

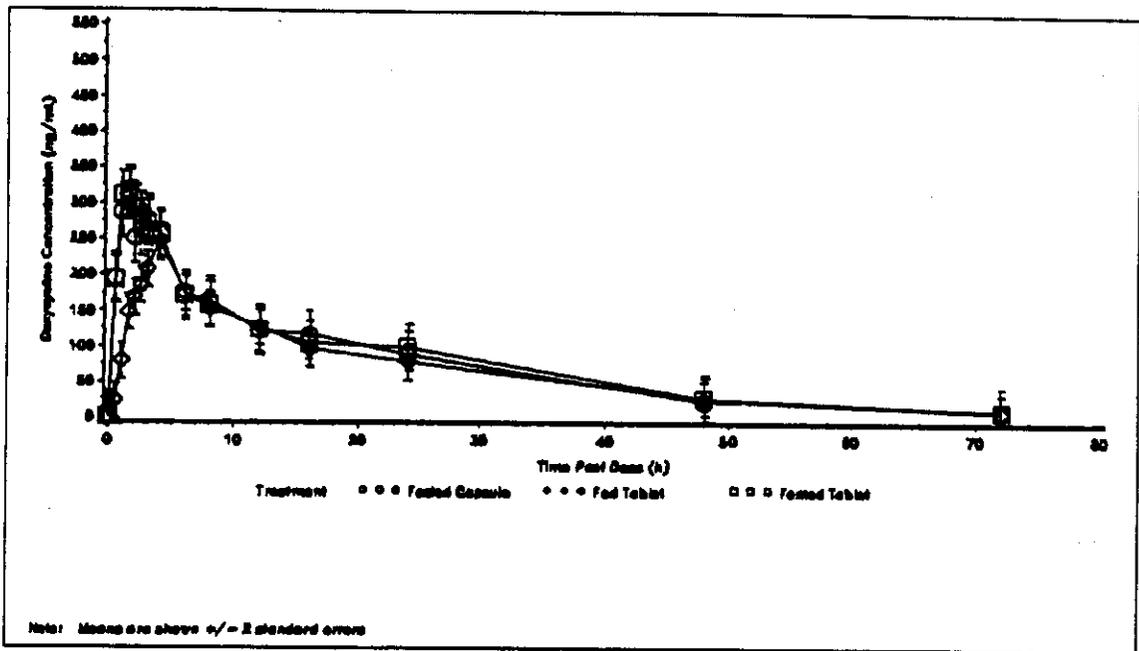


Figure 1: Linear Plot of Mean Plasma Concentration-Time Profile Per Protocol Subjects

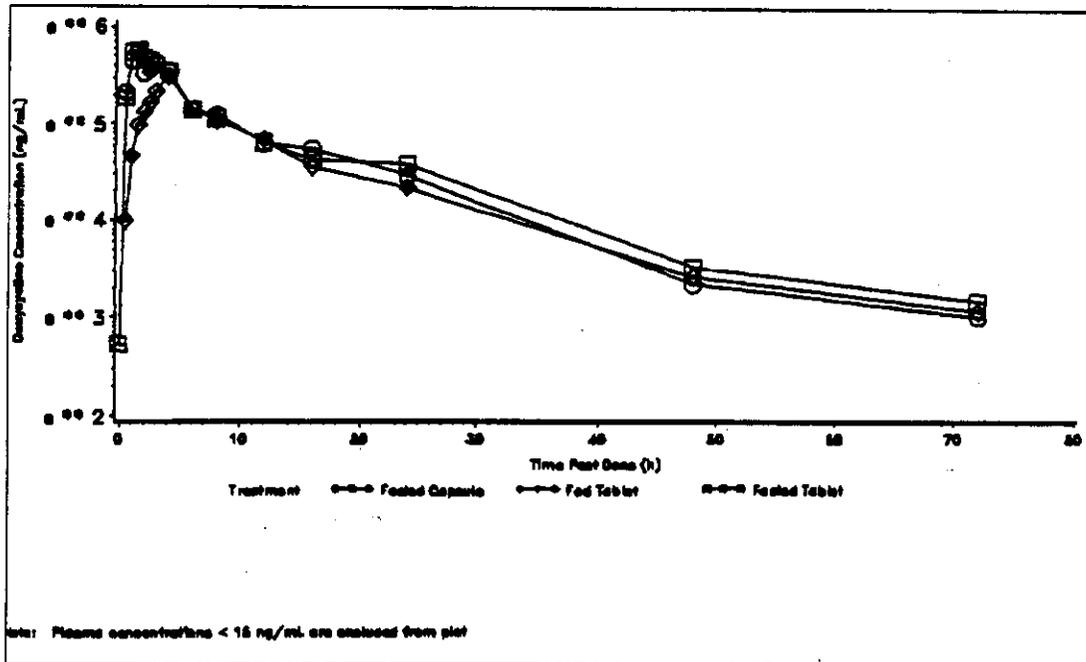


Figure 2: Semi-logarithmic Plot of Mean Plasma Concentration-Time Profile Per Protocol Subjects

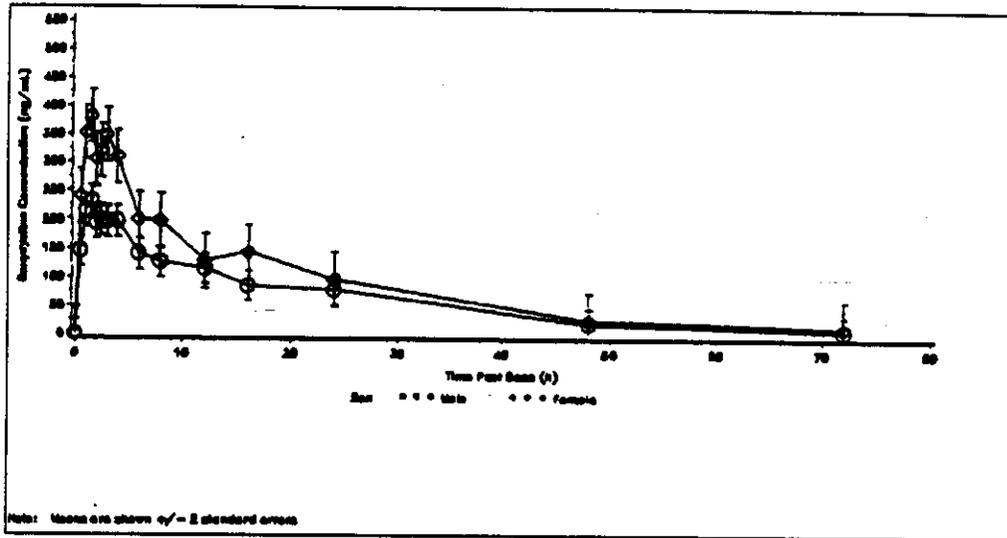


Figure 3: Linear Plot of Mean Plasma Concentration-Time Profile for Fasted Capsule Treatment by Gender Per Protocol Subjects

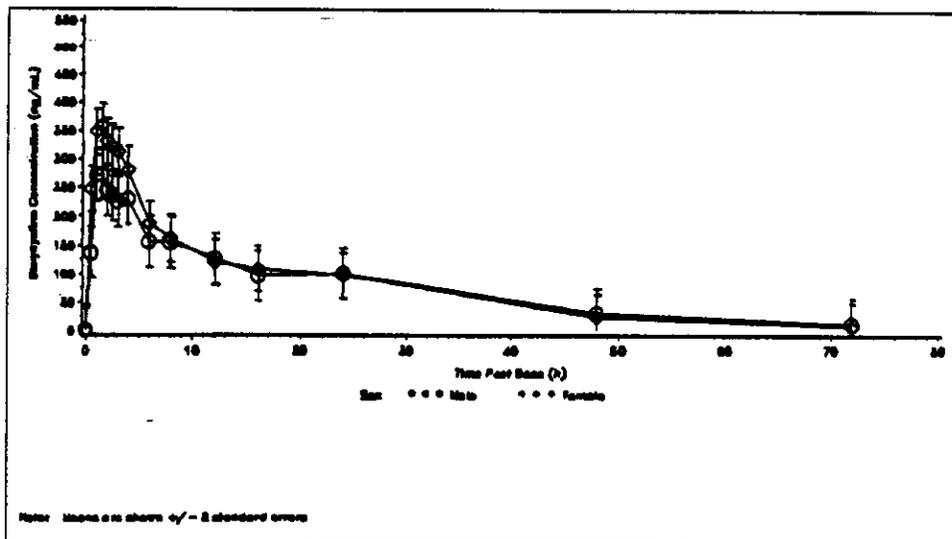


Figure 4: Linear Plot of Mean Plasma Concentration-Time Profile for Fasted Tablet Treatment by Gender Per Protocol Subjects

The capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. The least squares mean was close to 100%, which indicates a high level of bioequivalence.

4.3 Analysis of Food Effect

Summary data for bioavailability (food effect) of the doxycycline tablet formulation taken with food compared to that of the doxycycline tablet taken in the fasting condition are given in Table 5. Pharmacokinetic parameters for the two conditions are presented in Table 6. Plasma concentrations for subjects in the two conditions are noted in Table 4 and Figures 1 and 2. Data are presented by gender in Figures 4 and 5.

The area under the curve extrapolated to infinity ($AUC_{0-\infty}$) for per-protocol patients in the fed tablet condition was 4969 ng.h/mL and for the fasted tablet condition, 5487 ng.h/mL (Table 6). The least squares mean ratio between the two was 91.5%, with the 90% confidence interval falling between 78.8% and 106.3%. Similar results were found for AUC_{0-t} . The same conclusions were reached using the ITT population.

C_{max} for per-protocol subjects in the fed tablet condition was 259 ng/mL and for the fasted tablet condition, 347 ng/mL (Table 6). The least squares mean ratio between the two was 75.0%, with the 90% confidence interval falling between 67.1% and 83.8% (Table 5). Results for the ITT cohort were similar.

For per protocol subjects, the mean t_{max} for doxycycline in plasma was 3.4 hours (range: — to — hours) post-dosing in the fed tablet condition and 1.4 hours (range: — to — hours) in the fasted tablet condition (Table 6).

For per protocol subjects, the $t_{1/2}$ ranged from — to — hours (with a mean of 20.3 hours) in the fed tablet condition and ranged from — to — hours (with a mean of 18.1 hours) in the fasted tablet condition.

Female subjects had a higher AUC and maximum concentration (C_{max}), a longer t_{max} , and a shorter $t_{1/2}$ than males. Gender differences in AUC, t_{max} , and $t_{1/2}$ appear to be more marked for the fed tablet condition compared to the fasted tablet condition. Conversely, for C_{max} , a more marked gender difference is seen in the fasted tablet condition compared to the fed tablet condition.

There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means for C_{max} fell below 70%. The AUC and C_{max} were lower and the t_{max} was higher in the fed state, indicating that food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

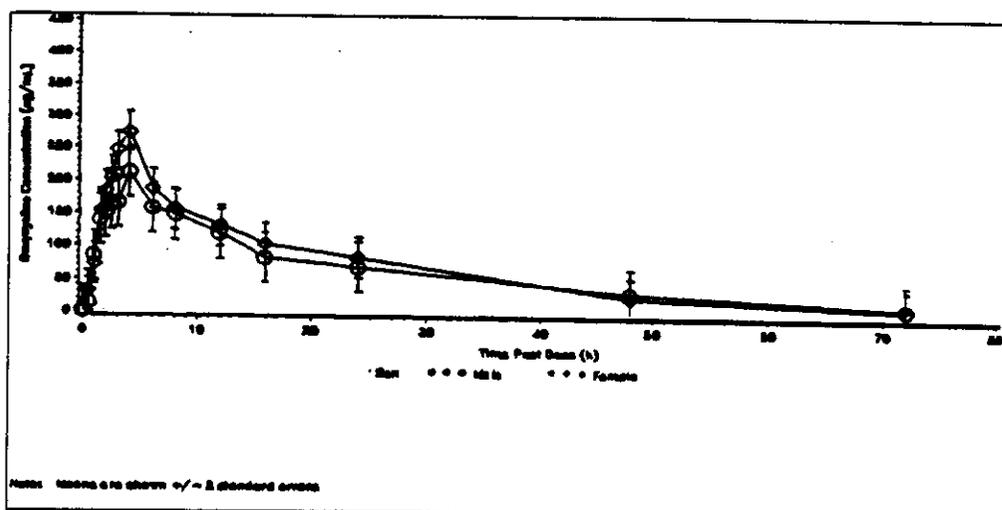


Figure 5: Linear Plot of Mean Plasma Concentration-Time profile for Fed Tablet Treatment by Gender Per Protocol Subjects

Table 5
Summary of Bioavailability (BA) Results: Statistics for Treatment Differences and Ratios

Parameter	Variable	Per Protocol			Intent-to-Treat				
		N	Least Squares Mean	90% Lower Confidence Limit	90% Upper Confidence Limit	N	Least Squares Mean	90% Lower Confidence Limit	90% Upper Confidence Limit
AUC 0-inf	F/T	19	91.5%*	78.8%*	106.3%*	19	91.2%	78.8%	105.5%
	F-T		-557.0	-1471.1	357.1		-564.5	-1455.5	326.5
AUC 0-t	F/T	19	86.0%*	73.3%*	101.0%*	19	85.9%	73.4%	100.5%
	F-T		-845.5	-1655.8	-35.2		-842.1	-1633.6	-50.5
Cmax	F/T	19	75.0%*	67.1%*	83.8%*	19	74.8%	67.1%	83.4%
	F-T		-88.8	-124.4	-53.1		-89.6	-124.6	-54.6
tmax	F/T**	19	1.75	1.25	2.50	19	1.75	1.00	2.50
	F-T		1.98	1.42	2.55		1.99	1.43	2.54
t 1/2	F/T	19	112.30%	95.86%	131.57%	19	112.69%	96.48%	131.62%
	F-T		2.50	-0.72	5.73		2.54	-0.60	5.69
lambda_z	F/T	19	89.032%	76.005%	104.292%	19	88.732%	75.978%	103.626%
	F-T		-0.004	-0.010	0.002		-0.004	-0.010	0.002

Table 6
Summary of Bioavailability (BA) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat		
			Males	Females	Total	Males	Females	Total
AUC 0-inf	F	N	9	10	19	9	10	19
		Arithmetic Mean	4883	5557	5238	4883	5557	5238
		Geometric Mean	4568	5359	4969	4568	5359	4969
	Coefficient of Variation (%)	41.5	29.7	34.7	41.5	29.7	34.7	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	5671	5984	5836	5671	5949	5824
Geometric Mean		5259	5700	5487	5259	5691	5493	
Coefficient of Variation (%)	45.6	32.7	38.0	45.6	31.2	37.1		
AUC 0-t	F	N	9	10	19	9	10	19
		Arithmetic Mean	4055	4392	4232	4055	4392	4232
		Geometric Mean	3713	4286	4004	3713	4286	4004
	Coefficient of Variation (%)	46.1	23.5	34.4	46.1	23.5	34.4	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	5069	5089	5079	5069	5091	5081
Geometric Mean		4616	4748	4685	4616	4780	4706	
Coefficient of Variation (%)	50.3	38.3	43.0	50.3	36.3	41.9		
Cmax	F	N	9	10	19	9	10	19
		Arithmetic Mean	243.6	297.2	271.8	243.6	297.2	271.8
		Geometric Mean	225.8	292.6	258.8	225.8	292.6	258.8
	Coefficient of Variation (%)	42.5	19.0	31.1	42.5	19.0	31.1	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	308.3	410.0	361.8	308.3	417.2	368.2
Geometric Mean		294.1	403.2	347.2	294.1	410.4	353.2	
Coefficient of Variation (%)	33.8	18.0	28.0	33.8	17.7	27.9		
tmax	F	N	9	10	19	9	10	19
		Arithmetic Mean	3.22	3.55	3.39	3.22	3.55	3.39
		Geometric Mean	2.70	3.33	3.01	2.70	3.33	3.01
	Coefficient of Variation (%)	65.9	35.4	49.5	65.9	35.4	49.5	
	T	N	9	10	19	9	11	20
		Arithmetic Mean	1.33	1.45	1.39	1.33	1.41	1.38
Geometric Mean		1.27	1.39	1.33	1.27	1.35	1.31	
Coefficient of Variation (%)	37.5	30.2	32.9	37.5	31.0	33.1		

Table 6
Summary of Bioavailability (BA) Results: Statistics for Pharmacokinetic Parameters by Treatment and Gender

Parameter	Treatment	Statistic	Per Protocol			Intent-to-Treat		
			Males	Females	Total	Males	Females	Total
$t_{1/2}$	F	N	9	10	19	9	10	19
		Arithmetic Mean	21.38	19.37	20.32	21.38	19.37	20.32
		Geometric Mean	20.71	18.25	19.38	20.71	18.25	19.38
	T	Coefficient of Variation (%)	26.1	38.3	32.0	26.1	38.3	32.0
		N	9	10	19	9	11	20
		Arithmetic Mean	18.70	17.48	18.06	18.70	17.20	17.88
lambda_z	Geometric Mean	18.18	16.81	17.44	18.18	16.57	17.28	
	Coefficient of Variation (%)	25.2	29.5	26.9	25.2	28.9	26.8	
	F	N	9	10	19	9	10	19
Arithmetic Mean		0.0346	0.0401	0.0375	0.0346	0.0401	0.0375	
Geometric Mean		0.0335	0.0380	0.0358	0.0335	0.0380	0.0358	
T	Coefficient of Variation (%)	27.2	32.4	30.6	27.2	32.4	30.6	
	N	9	10	19	9	11	20	
	Arithmetic Mean	0.0392	0.0429	0.0412	0.0392	0.0434	0.0415	
lambda_z	Geometric Mean	0.0381	0.0412	0.0397	0.0381	0.0418	0.0401	
	Coefficient of Variation (%)	25.2	28.9	27.1	25.2	27.4	26.4	

5. DISCUSSION AND CONCLUSIONS

The objectives of this study were to test for bioequivalence between the currently-marketed doxycycline hyclate 20 mg capsule and a doxycycline hyclate 20 mg tablet; and to evaluate possible food effects in the pharmacokinetic profile of doxycycline hyclate 20 mg tablets.

The capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. The least squares mean was close to 100%, which indicates a high level of bioequivalence.

AUC and C_{max} were higher, and $t_{1/2}$ was shorter in females than males. These gender differences appear to be more marked for the fasted capsule condition compared to the fasted tablet condition as summarized in the following Table 7:

Table 7: Summary of Gender Analysis

Study	Entity	Parameter	Male (M)	Female (F)	Comments
Bioequivalence	Fasted Capsule	AUC _{0-∞}	4925 ng.h/mL	6025 ng.h/mL	F22.3%>M
	Fasted Tablet	AUC _{0-∞}	5259 ng.h/mL	5700 ng.h/mL	F8.4%>M
	Fasted Capsule	C _{max}	243.6 ng/mL	418.1 ng/mL	F71.6%>M
	Fasted Tablet	C _{max}	294.1 ng/mL	403.2 ng/mL	F37.1%>M
	Fasted Capsule	t _{1/2}	22.0 hr	16.7 hr	M31.7%>F
	Fasted Tablet	t _{1/2}	18.7 hr	17.5 hr	M6.9%>F
Bioavailability (Food Effect)	Fed Tablet	AUC _{0-∞}	4568 ng.h/mL	5359 ng.h/mL	F17.3%>M
	Fasted Tablet	AUC _{0-∞}	5259 ng.h/mL	5700 ng.h/mL	F8.4%>M
	Fed Tablet	C _{max}	225.8 ng/mL	292.6 ng/mL	F29.6%>M
	Fasted Tablet	C _{max}	294.1 ng/mL	403.2 ng/mL	F37.1%>M
	Fed Tablet	t _{1/2}	21.4 hr	19.4 hr	M10.3%>F
	Fasted Tablet	t _{1/2}	18.7 hr	17.5 hr	M6.9%>F
	Fed Tablet	t _{max}	3.22 hr	3.55 hr	F10.3%>M
Fasted Tablet	t _{max}	1.33 hr	1.45 hr	F9.0%>M	

There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. The AUC and C_{max} were lower and the t_{max} was higher in the fed state, indicating that food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

Female subjects had a higher AUC and maximum concentration (C_{max}), a longer t_{max}, and a shorter t_{1/2} than males. Gender differences in AUC and t_{1/2} appear to be more marked for the fed tablet condition compared to the fasted tablet condition. Conversely, for C_{max},

a more marked gender difference is seen in the fasted tablet condition compared to the fed tablet condition (Table 7).

Final Conclusions

The capsule and tablet formulations of doxycycline are bioequivalent since the 90% confidence interval for the ratio of means for both AUC and C_{max} fell within 80%-125%. There is a food effect since the 90% lower confidence limit for the ratio of means (fed to fasted) for AUC fell below 80% and the 90% lower confidence limit for the ratio of means (fed to fasted) for C_{max} fell below 70%. Food decreases the rate and extent of absorption and delays the time at which maximal concentrations are reached.

6. COMMENTS:

- ❖ The sponsor discussed differences in pharmacokinetic parameters between males and females in several places. However, in their demographic distribution table, they did not report individual or mean weight of the male and female patients. Given that mean female weight is 1/3rd less than mean male weight, a weight normalized analysis of the individual pharmacokinetic parameters could have eliminated the observed differences in pharmacokinetic parameters between male and female subpopulation and rendered the following comments redundant.
- ❖ In both bioequivalence and food effect bioavailability studies, it was found that AUC and C_{max} were higher, and $t_{1/2}$ was shorter in females than males. It is an apparent anomaly to the conventional relationship between AUC and $t_{1/2}$ which should be proportional to each other.
- ❖ Though AUC and C_{max} were higher in females than males, the extent of the difference does not call for recommendation for any dose adjustment.
- ❖ Comments pertaining to gender differences in the subheading *Gender* under **Clinical Pharmacology** labeling should be eliminated.

7. LABELING COMMENTS:

Following modifications have been proposed in the "Clinical Pharmacology" section of the labeling. "Strikeout" means suggested deletions and "Shading" suggests insertion of new text.

Pharmacokinetics

The pharmacokinetics of doxycycline following oral administration of Periostat® were investigated in 4 volunteer studies involving 107 adults. Additionally, doxycycline pharmacokinetics have been characterized in numerous scientific publications.² Pharmacokinetic parameters for Periostat® following single oral doses and at steady-state in healthy subjects are presented as follows:

DRAFT

Genders

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/s/

Tapash Ghosh
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