CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208253Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA(s): 208253	Submission Date(s): 06/26/2015
Drug	Doxycycline hyclate
OCP Reviewer	Dakshina M. Chilukuri, PhD
OCP Team Leader	Seong H. Jang, PhD
OCP Division	DCP4
OND Division	DAIP
Sponsor	Aqua Pharmaceuticals
Formulation/Strength	75 mg Capsules
Indication(s)	Rickettsial infections, sexually transmitted infections, respiratory tract infections, specific bacterial infections, ophthalmic infections, anthrax, including inhalational anthrax (post-exposure), alternative treatment for selected infections when penicillin is contraindicated, adjunctive therapy in acute intestinal amebiasis and severe acne, prophylaxis of malaria

1. EXECUTIVE SUMMARY

This NDA from Aqua Pharmaceuticals is for new strengths of the listed drug (LD) Vibramycin® (doxycycline hyclate capsules, USP) Capsules (NDA 050007, Pfizer). Aqua proposes to introduce a new dosage strength of 75 mg to provide flexibility and ease of dosing. The 75 mg dosage strength falls within the approved dosing regimens for the approved Listed Drug (LD). Aqua is seeking approval of the 75 mg dosage strength for the same indications as the currently approved LD.

Aqua completed two pharmacokinetic studies (Study 11060201 and 11060202) to provide a clinical bridge to the Agency's finding of efficacy and safety for the LD, support the 505(b)(2) NDA for the new 75 mg dosage strength and evaluate the effect of food on systemic absorption. Study 11060201 successfully demonstrated bioequivalence of Aqua's Doxycycline Hyclate Capsules, 150 mg to the listed drug (LD) Vibramycin® Hyclate (doxycycline hyclate capsules, USP) Capsules (NDA 050007, Pfizer). Aqua is requesting a waiver from conducting *in vivo* bioequivalence studies of the Doxycycline Hyclate Capsules, 75 mg based on the (b) (4) favorable dissolution profile comparison of the 75 mg and 150 mg capsule dosage strengths. The waiver request will be reviewed by Dr. Gerlie Gieser, ONDP.

Doxycycline is completely absorbed after oral administration. Following administration of a single 300 mg dose of Aqua's Doxycycline Hyclate Capsules to adult volunteers, average peak plasma doxycycline concentrations were approximately 2.8 mcg/mL, decreasing to 1.0 mcg/mL at 24 hours. The mean Cmax of doxycycline is approximately 20% lower and the Tmax was extended by approximately 2 hours following a single dose of Aqua's Doxycycline Hyclate Capsules, 150 mg with a high fat meal compared to fasted conditions. However, there was no change in overall bioavailability, with the 90% CI for both AUC0-t and $AUC_{0-\infty}$ falling within the range of 80%-125%. Therefore, it is proposed that doxycycline hyclate capsules can be taken without regard to meals.

The pivotal BE study conducted by the applicant was reviewed and it is agreed that the test formulation of Doxycycline Hyclate Capsule, 150 mg (Aqua Pharmaceuticals) meets the 90% CI criterion for log transformed AUC_{0-t}, AUC_{0-inf}, and Cmax and has therefore shown equivalent bioavailability to a similar dosage of the LD, Vibramycin® (doxycycline hyclate) capsule, 100 mg (Pfizer Labs).

2. RECOMMENDATIONS

The clinical pharmacology information provided by the applicant in support of the 505 (b)(2) application is found to be acceptable and supports the approval of Doxycycline 75 mg capsules pending the biowaiver review and an agreement on the labeling.

Individual Study Reviews

STUDY NO. 11060201

STUDY TITLE: A Study to Evaluate the Relative Bioavailability of (b) (4) Doxycycline Hyclate Capsules 150 mg (AQUA Pharmaceuticals LLC) compared to an Equal Dose of Vibramycin® (doxycycline hyclate) Capsules (Pfizer Labs) in Healthy Volunteers under Fasted Conditions

OBJECTIVE: The purpose of this study was to evaluate the relative bioavailability of a test formulation of doxycycline hyclate capsules, 150 mg (AQUA Pharmaceuticals) compared to an equal dose of the FDA Orange Book listed reference formulation, 100 mg Vibramycin® (doxycycline hyclate) capsules (Pfizer Labs) under fasted conditions in healthy volunteers.

METHODOLOGY: This was a randomized, single-dose, two-treatment, two-period, crossover study under fasting conditions comparing equal doses of the test and reference products. The study was conducted with 26 (22 completing) healthy adult subjects. In each period of the study, a single 300 mg dose of doxycycline was administered to subjects following an overnight fast of at least 10 hours. The test formulation was doxycycline hyclate capsule, 150 mg (Aqua Pharmaceuticals) and the reference formulation was Vibramycin® (doxycycline hyclate) capsule, 100 mg (Pfizer Labs). Subjects received the test product as 2 x 150 mg capsules in one of the study periods and the reference product as 3 x 100 mg capsules in the other study period, according to the randomization schedule. Subjects were confined at the clinical facility from at least 10 hours prior to dosing until after the 24 hour blood collection and returned to the clinical facility for pharmacokinetic sampling at 36, 48 and 72 hours. The interval between doses was 14 days.

Blood samples were collected at pre-dose and at intervals over 72 hours after dosing in each period. Statistical analysis using average bioequivalence methodology was performed to evaluate the relative bioavailability of the test formulation to that of the reference product under fasted conditions. Equivalence was determined based on the confidence intervals for the major pharmacokinetic parameters, AUC_{0-t}, AUC_{0-inf} and Cmax, for doxycycline.

DURATION OF TREATMENT: In each study period, a single 300 mg dose of doxycycline hyclate capsules was administered to subjects following an overnight fast of at least 10 hours. The subjects received the test (2 x 150 mg capsules) and reference treatments (3 x100 mg capsules) according to the randomization schedule. Each dose was separated by a 14 day interval. The study began dosing on (b) (4) and was completed on (b) (4).

STATISTICAL METHODS: Twenty (20) blood samples were collected from each subject during each period of the study: prior to dosing, then at 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36 48 and 72 hours after dosing for analysis of plasma doxycycline concentrations. The analytical data was used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, Cmax, Tmax, K_{el} and $T_{½}$.

Bioanalytical Analysis: The bioanalytical analysis was conducted at (b) (4)

(b) (4)

SUMMARY OF RESULTS:

Bioanalytical Validation: The following section details the bioanalytical method validation for the analysis of doxycycline in human EDTA plasma samples. The methodology employed a protein precipitation procedure followed by UPLC-MS/MS analysis. The method was validated on an AB Sciex 5000 based LC-MS/MS system (b) (4) LC/MS/MS (b) (4)) and has the following performance characteristics.

Analyte	Doxycycline
Internal Standard (IS)	Oxytetracycline
Method Description	Protein precipitation with acetonitrile and 1% formic acid dilution and reverse phase UPLC-MS/MS analysis.
Limit of Quantitation, Precision, Accuracy	100.00 ng/mL, 4.9%, 94.9%
Average Recovery of Drug (%)	88.5
Average Recovery of IS (%)	84.2
Standard Curve Concentrations (ng/mL)	100.00 – 5000.00
QC Concentrations (ng/mL)	300.00, 800.00, 4000.00
QC Intra-Run Precision Range (%)	4.5, 2.9, 3.1
QC Intra-Run Accuracy Range (%)	97.3, 100.3, 99.6
QC Inter-Run Precision Range (%)	5.0, 9.3, 6.3
QC Inter-Run Accuracy Range (%)	97.2, 104.4, 101.5
4°C Temperature	24 hours
Ambient Temperature	24 hours
Stock Stability @ 4°C	213 days
Auto Sampler @ 10°C Processed Stability	4 days
Freeze-Thaw Stability	3 cycles
Frozen Stability -20°C	5 days
Frozen Stability -80°C	5 days
Dilution Integrity 5-Fold and 10-Fold (% Accuracy)	104.3, 96.3
Selectivity	No interfering peaks noted in blank plasma samples
Instrument Precision (%)	1.7

Pharmacokinetic Results: Mean plasma concentration of doxycycline versus time plots are presented in Figure 1. Twenty-six (26) subjects were dosed in Period I, and twenty-two (22) subjects completed both periods of the study.

Figure 1. Mean Concentration versus Time Plot: Doxycycline

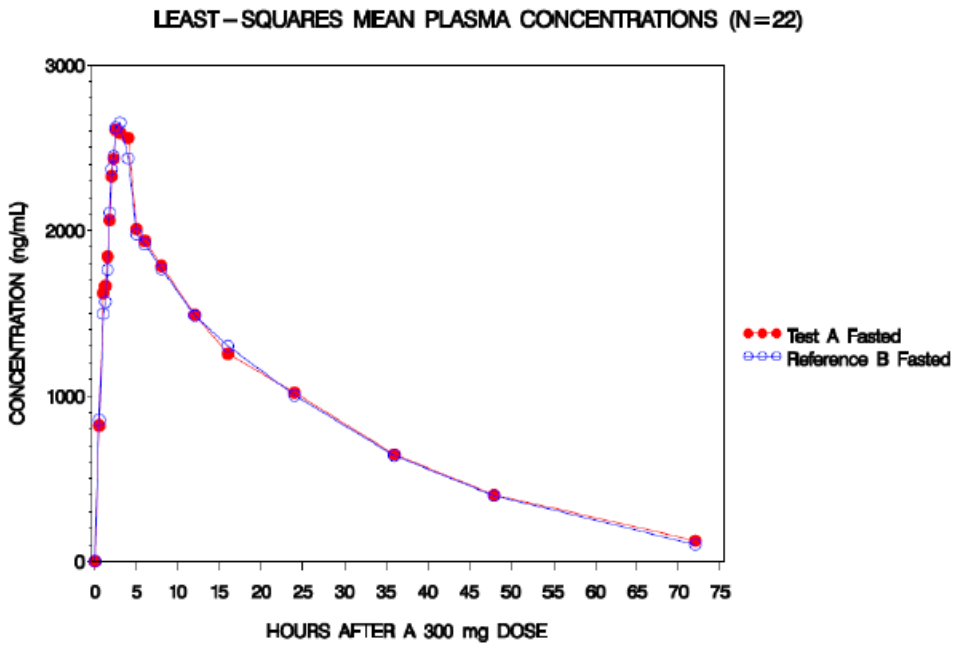

Table 1. Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Doxycycline (N = 22)

Parameter	Treatment A (test)	Treatment B (reference)	Ratio	CI*	Intra-Subject %CV
AUC_{0-t} (ng·hr/mL)	57155.04	55587.75	1.0282	0.9497 - 1.1132	15.2958
AUC_{0-inf} (ng·hr/mL)	63017.18	61525.97	1.0242	0.9401 - 1.1159	16.5192
Cmax (ng/mL)	2756.47	2734.26	1.0081	0.9379 - 1.0836	13.8872
* Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.					

Treatment A (test): 2 x 150 mg Doxycycline Hyclate Capsules (AQUA Pharmaceuticals)
Treatment B (reference): 3 x 100 mg Vibramycin® (doxycycline hyclate) Capsules (Pfizer Labs)

CONCLUSION: Based on the statistical analysis of doxycycline PK parameters, the test formulation of doxycycline hyclate capsule, 150 mg (Aqua Pharmaceuticals) meets the 90% CI criterion for log transformed AUC_{0-t}, AUC_{0-inf}, and Cmax and has therefore shown equivalent bioavailability to a similar dosage of the reference formulation, Vibramycin® (doxycycline hyclate) capsule, 100 mg (Pfizer Labs). There were no serious adverse events reported during this study. Both the test and reference products were well-tolerated during the study.

STUDY NO. 11060202

STUDY TITLE: A Study to Compare the Relative Bioavailability of (b) (4) Doxycycline Hyclate Capsules 150 mg (AQUA Pharmaceuticals LLC) under Fasted and Non-Fasted Conditions

OBJECTIVE: The purpose of this study was to evaluate the relative bioavailability of a test formulation of doxycycline hyclate capsules, 150 mg (AQUA Pharmaceuticals) under fasted and non-fasted conditions in healthy volunteers.

METHODOLOGY: This was a randomized, single-dose, two-treatment, two-period, crossover study under fasting and non-fasting conditions. The study was conducted with 26 healthy adult subjects. In one period of the study, a single doxycycline hyclate 150 mg capsule was administered after an overnight fast of at least 10 hours. In the other period, a single doxycycline hyclate 150 mg capsule was administered following a standardized high fat breakfast. The order of administration followed a two sequence randomization schedule. The test formulation was doxycycline hyclate capsule, 150 mg (Aqua Pharmaceuticals). Subjects were confined at the clinical facility from at least 10 hours prior to dosing until after the 24 hour blood collection and returned to the clinical facility for pharmacokinetic sampling at 36, 48 and 72 hours. The interval between doses was 14 days.

Blood samples were collected at pre-dose and at intervals over 72 hours after dosing in each period. Statistical analysis using average bioequivalence methodology was performed to evaluate the relative bioavailability of the test formulation when taken after food compared to when taken in the fasted state. The effect of food was determined based on the confidence intervals for the major pharmacokinetic parameters, AUC_{0-t}, AUC_{0-inf} and Cmax, for doxycycline.

NUMBER OF SUBJECTS: A total of 26 healthy adult subjects were enrolled, and all 26 subjects completed the study.

DURATION OF TREATMENT: In one period of the study, a single doxycycline hyclate 150 mg capsule was administered after an overnight fast of at least 10 hours. In the other period, a single doxycycline hyclate 150 mg capsule was administered following a standardized high fat breakfast. The order of administration followed a two sequence randomization schedule.

STATISTICAL METHODS: Twenty (20) blood samples were collected from each subject during each period of the study: prior to dosing, then at 0.5, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36* 48* and 72* hours after dosing (* return samples) for analysis of plasma doxycycline concentrations. The analytical data was used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, Cmax, Tmax, K_{el} and $T_{½}$.

Bioanalytical Analysis: The bioanalytical analysis was conducted at (b) (4)

SUMMARY OF RESULTS:

Bioanalytical Validation: The following section details the bioanalytical method validation for the analysis of doxycycline in human EDTA plasma samples. The methodology utilizes a technique of protein precipitation followed by high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS). The method was validated on an AB Sciex 5000 based LC-MS/MS system ((b) (4)), and has the following performance characteristics.

Parameter	Data
Analyte	Doxycycline
Internal Standard	Oxytetracycline
Method Description	Samples (0.2 mL) are purified by the addition of acetonitrile (0.4 mL) and diluted 1:1 with 1% formic acid prior to HPLC-ESI+MS/MS analysis using a Waters XBridge C18 column employing a gradient mobile phase.
Limit of Quantitation, Precision, Accuracy	25.00 ng/mL, 5.4%, 102.8%
Average Recovery of Drug (%)	74.6%
Average Recovery of IS (%)	88.2%
Standard Curve Concentrations (ng/mL)	25.00 – 2,000.00
QC Concentrations (ng/mL)	75.00, 500.00, 1600.00
QC Intra-Run Precision Range (%)	1.7– 3.8%
QC Intra-Ray Accuracy Range (%)	93.4 – 97.3%
QC Inter-Run Precision Range (%)	9.3 – 11.6%
QC Inter-Run Accuracy Range (%)	99.3 – 101.9%
Refrigerated Temperature (4°C)	46 hours
Room Temp/Bench-top Temperature	46 hours (light protected), 15 hours (light exposed)
Stock Stability (days) (4°C)	39 days
Working Standard Stability (days) (4°C)	39 days
Auto-Sampler Processed Stability (10°C)	5 days
Processed Stability (days) (4°C)	5 days
Freeze-thaw Stability (cycles)	4 cycles
Long-Term Storage Stability (-20°C)	23 days
Long-Term Storage Stability (-80°C)	241 days
Dilution Integrity	6400 ng/mL diluted 5x and 10x
Selectivity	No interfering peaks noted in blank plasma

Pharmacokinetic Results: Mean plasma concentration of doxycycline versus time plots are presented in Figure 2. Twenty-six (26) subjects were dosed in Period I, and all twenty-six (26) subjects completed both periods of the study. There are 26 sets of data for doxycycline for this study.

Figure 2. Mean Concentration versus Time Plot: Doxycycline

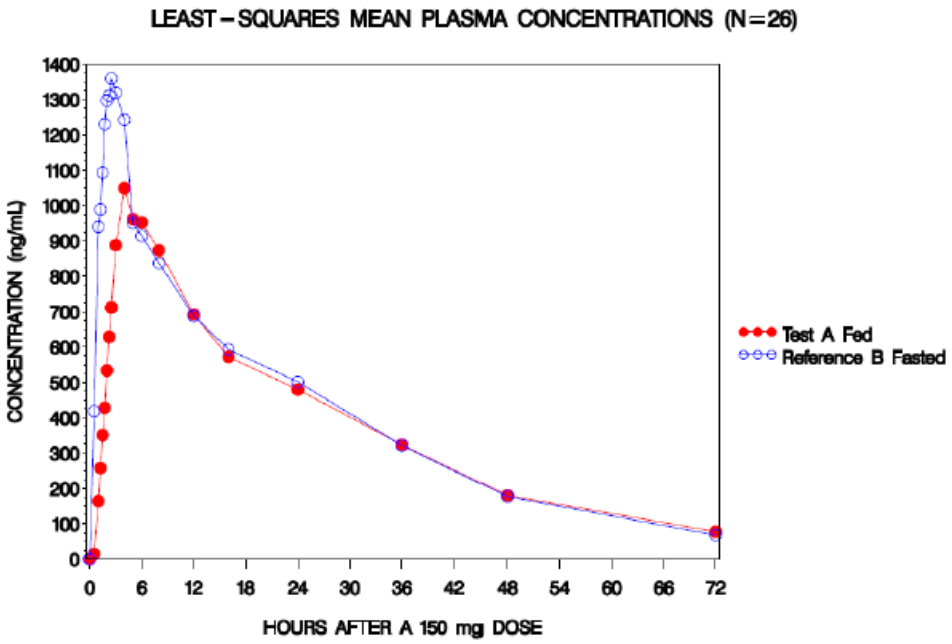

Table 2. Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data: Doxycycline (N = 26)

Parameter	Treatment A (fed)	Treatment B (fasted)	Ratio	CI*	Intra-Subject %CV
AUC_{0-t} (ng·hr/mL)	26121.83	28080.14	0.9303	0.8924 - 0.9697	8.7645
AUC_{0-inf} (ng·hr/mL)	28191.58	29757.49	0.9474	0.9040 - 0.9929	9.9060
Cmax (ng/mL)	1106.38	1386.70	0.7979	0.7462 - 0.8530	14.1644
* Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.					

Treatment A (fed): 1 x 150 mg Doxycycline Hyclate Capsule (AQUA Pharmaceuticals) after high fat breakfast
Treatment B (fasted): 1 x 150 mg Doxycycline Hyclate Capsule (AQUA Pharmaceuticals) after an overnight fast

CONCLUSION: When dosing doxycycline hyclate capsule, 150 mg (Aqua Pharmaceuticals) after a high fat breakfast, Cmax is reduced by approximately 20% compared with the fasted state and Tmax was extended by about 2 hours. However, there was no change in the extent of bioavailability, with the 90% CI for both AUC_{0-t} and AUC_{0-inf} falling within the range 80-125%. As this drug is intended for chronic rather than acute usage, then this decrease in maximum exposure after a single dose is not significant with respect to clinical efficacy. Therefore, it is proposed that doxycycline hyclate capsules, 150 mg (Aqua Pharmaceuticals) can be taken without regard to meals. There were no serious adverse events reported during this study. Both the test and reference treatments were well-tolerated during the study.

Proposed package insert: Available separately.

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/s/

DAKSHINA M CHILUKURI
01/07/2016

SEONG H JANG
01/08/2016

M E M O R A N D U M

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

DATE: 9/11/2015

TO: Division of Anti-Infective Products
Office of Antimicrobial Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208253

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services	3760 Pecos McLeod, Las Vegas, NV
Analytical		(b) (4)

Nicola M. Nicol -S

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Date: 2015.09.11 13:18:51 -04'00'

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NICOLA M FENTY-STEWART
09/11/2015